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CONTENTS

CORRECTIONS

To P. P. von Weimarn's Paper "The Precipitation Laws"

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LITERARY REFERENCES RELATING TO FIGURES*

To figures 1–7. P. P. *von Weimarn* and *S. Otsuka.* Laboratory for Physical Chemistry of the Kyoto Imperial University (Director: Prof. *Y. Osaka*). 1922. In extenso as yet unpublished. For some data, see: *P. P. von Weimarn.* Koll.-Zeitschr. *33.* 234–237 (1923).

To figures 8–9. P. P. *von Weimarn* and *H. Hori.* Laboratory for Physical Chemistry of the Kyoto Imperial University. 1923. Unpublished.

To figures 10–13. P. P. *von Weimarn* and *S. Morishima.* Laboratory for Physical Chemistry of the Kyoto Imperial University. 1923. In extenso as yet unpublished. For some data, see: *P. P. von Weimarn.* Koll.-Zeitschr. *36.* 10 (1925).

To figures 14–17. P. P. *von Weimarn, K. Aoki,* and *S. Kataoka.* Laboratory for Physical Chemistry of the Kyoto Imperial University. 1923. In extenso as yet unpublished. For some data, see: *P. P. von Weimarn.* Revue générale des Colloides. 2 année. pp. 199–200 (1924); Koll.-Zeitschr. *36.* 239; *37.* 84 (1925).

To figures 18–23. P. P. *von Weimarn* and *S. Utzino.* Memoirs of the College of Science, Kyoto Imperial University. Series A. *8.* 291 (1925); Koll.-Zeitschr. *36.* 265 (1925); *P. P. von Weimarn.* Koll.-Zeitschr. *37.* 151 (1925).

To figure 24. P. P. *von Weimarn* and *S. Utzino.* Laboratory for Physical Chemistry of the Kyoto Imperial University. 1924. Unpublished.

To figure 25. P. P. *von Weimarn, T. Shochara,* and *S. Takashige.* Laboratory for Physical Chemistry of the Kyoto Imperial University. 1922. In extenso as yet unpublished. For some data, see: *P. P. von Weimarn.* Koll.-Zeitschr. *33.* 242 (1923); Reports of the Imperial Industrial Research Institute of Osaka. *5.* 52 (1925).

* In the original manuscript received from the author, the figures have been arranged in a series of tables containing, at the head, the explanations of the figures, and at the foot the literary references relating to the figures; on reducing the scale of the figures, etc., the above form of presentation has been altered: the explanations of figures have all been collected together and printed in a separate page (p. 236), and the literary references relating to figures happened to be entirely omitted; it must be pointed out that the paper has been printed without any proofs having been read by the author himself.

The form of the equations given in p. 218 must be corrected, comformably to the author's MS, in the following manner:

$$ y = k_1 x^- \left(1^{\frac{k_2}{x^{n_1 \cdot t}}} - 1 \right)^{-1} $$

THE DISCOVERY AND PROPERTIES OF HAFNIUM

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CONTENTS

1

THE DISCOVERY OF HAFNIUM AND THE QUANTUM THEORY
OF ATOMIC STRUCTURE

1. The rare earths. The complexity of Marignac's ytterbium

In the course of the first half of the nineteenth century the
problem of the atomic weight determination of most of the
elements was taken up for the first time. The next step
which suggested itself was to search after possible regularities
which might exist between the atomic weights and the chemical
characteristics of the elements. As is well known, Mendelejeff
and Lothar Meyer first attacked successfully this problem to
which additions from many sources have since been made gradu-
ally. We find when proceeding further in the order of increas-
ing atomic weights of the elements, that the chemical properties
change completely, but find later that the series periodically
repeats itself. This periodicity does not occur, of course, without
irregularities. After iron appear two elements, nickel and
cobalt, which are closely related to each other, and further on
ruthenium as well as osmium are followed by two intimately
related elements and finally the most striking irregularity lies
in the appearance of a large group of closely related elements,
those of the rare earths after barium. To have ignored with
gifted intuition these irregularities, when stating that funda-
mental connection between the chemical properties of the ele-
ments which has proved to be so important and instructive to
us to-day, was one of the greatest services of the founders of the
periodic system of the elements. Later in the course of the
development of the system, the question of the source of the
irregularities mentioned before, the appearance of the triads
and the group of the rare earths naturally thrust itself repeatedly
before the attention of scientists. That such irregularities can
appear was somewhat disturbing because after iron besides nickel
and cobalt there could follow other rare and as yet unknown
elements and also other triads, as yet unknown, and such could
also appear at other places and thus the number of elements
could be considerably greater than would follow from the peri-
odic system. In the group of the rare earths Mendelejeff con-

sidered the possibility of a larger number of elements and estimated the number of members of this group—of which 4 were known then—to be 20.   Moseley performed the greatest service to science by eliminating this uncertainty with a single stroke. The linear relationship discovered by him between the atomic number and the square root of the frequency of the characteristic Röntgen rays of an element enabled him to state exactly the number of elements between hydrogen and uranium.   It is clearly borne out that there are no other "triads" in this region except those already known, that the "triads" in reality contain only three members and further that between barium and tantalum in the region where the rare earths lie, there are only 16 elements—having the atomic numbers 57 to 72, both inclusive.   Of these elements 14 were known at the time of Moseley's discovery.   To have discovered and isolated nearly all of the rare earths without further theoretical guidance, in spite of their great similarity and the great rarity of some of these, is one of the most brilliant accomplishments that experimental chemistry has ever produced.   Of these 14 rare earths those with atomic numbers 70 and 71 were discovered last.   In the year 1878 Marignac isolated from the old erbium earth a new colorless earth slightly more basic than the others which was named ytterbium.   In 1905 in the course of a systematic investigation on the separation of the rare earths Auer von Welsbach (2, 3) found that ytterbium was a mixture of two elements and also specified the method suitable for their separation. Then in 1907 Auer von Welsbach (4) published the optical spectrum of both constituents which, as we know from researches performed in Siegbahn's laboratory (24), have the atomic numbers 70 and 71, and for which he proposed the names aldebaranium and cassiopeium.   Shortly previous to this publication (50) Urbain announced similar results and proposed the names neoytterbium and lutecium for the two constituents of ytterbium.   The International Committee on atomic weights adopted the names ytterbium and lutecium.[1]   The possibility seemed not

[1] See *J. Am. Chem. Soc.*, **36**, +588 (1914): Ber. **47**, 8 (1914). See also the report of the German committee (Ber. **57**, 5, 1924) in which the consideration of the nomenclature is taken up in view of new evidence.

improbable to both investigators that Marignac's ytterbium—
which consisted of about 90 per cent of the element 70 and 10
per cent of the element 71, as we know from the later researches
of Auer von Welsbach—might contain yet a third still more
easily soluble element than the two constituents already known.
Auer von Welsbach started with 200 kgm. of gadolinite and
secured after a fractional crystallization during several years one-
half gram of the final liquor which, however, consisted entirely of
cassiopeium and which showed no trace of the other supposed con-
stituent; the latter, had it been present in ytterbium, should have
been enriched in this fraction.   Urbain (53) on the other hand be-
lieved that he had discovered the third constituent of Marig-
nac's ytterbium in the year 1911.   In his final liquor there
appeared 21 new spectral lines which he had not previously
observed and at the same time the paramagnetism of his prep-
aration decreased very considerably compared with that of the
element 71.   The paramagnetism of this sample was found to
be only between one-third and one-fourth of the preparation
supposed to contain the element 71 in pure state.   On the
basis of this observation Urbain (53) announced in 1911 the
discovery of a new rare earth for which he proposed the name
celtium.   Partly from the appearance of strong spectral lines
and still more from the considerable decrease of the magnetic
susceptibility we must conclude that Urbain's preparation
must have contained a considerable amount of celtium.   Eleven
years later we learn from a communication of Dauvillier (21)
that in addition to the familiar X-ray lines of the elements 70
and 71 those of the elements 69 and 72 have also been recognized
in Urbain's preparation.   Dauvillier explained the appearance
of the two extraordinarily weak lines as due to the presence of a
trace of the element which Urbain believed to have discovered
on the basis of the observed optical lines.   (Cet élément a
été découvert par M. G. Urbain dans la préparation que nous
avons étudiée grace a l'apparition d'un groupe de lignes in-
connues dans le spectra d'arc.")   From a later publication of
Dauvillier (22) we also learn, that by this trace about 1/10,000
is to be understood.   It is surprising that the discrepancy be-

tween the observation of strong optical spectral lines and of a very significant decrease of the paramagnetism on the one hand and the observation of these extremely weak X-ray lines on the other was not noticed. Moreover we read in a communication of Urbain (54) added to that of Dauvillier that now (after the discovery of celtium) "the question of the composition of the former ytterbium of Marignac is settled," ("la question des constituents de l'ancien ytterbium de Marignac est réglee").

This was the state of this question in 1922, when the quantum theory of atomic structure (12) enabled me to make a definite assertion as regards the characteristics of the element 72. This assertion was in full contradiction to the view that the element 72 should be the third constituent of Marignac's ytterbium and thus lead to the discovery of the true element 72, an element which was indeed a constituent of an "old element," but of "zirconium" and not of "ytterbium."

2. The element 72 and the quantum theory of atomic structure

All the older attempts to explain the periodic system were unsuccessful. Only after the discovery of the electron did a more hopeful method of explanation appear possible, and Sir J. J. Thomson was the first to attempt to reduce the periodicity in the chemical characteristics to a periodic arrangement of the electrons in atoms. At this time a closer pursuit of this idea was frustrated by a lack of knowledge concerning the arrangement of electrons in the atom. The proposal of the nuclear atom by Rutherford which was followed quickly by the foundation by Bohr of the quantum theory of atomic structure gave the necessary impulse. This development which leads also to a rational explanation of the periodicity in the chemical characteristics of the elements as they show themselves in Mendelejeff's system, was successfully accomplished by Bohr in 1922. As regard the question of position, Bohr asked how the electrons group themselves about the atomic nucleus in the atoms of different elements and what changes the grouping of the electrons suffer as one goes from element to element. The rational use of the laws of the quantum theory led him to the answer

to this question and the numbers in the table shows his results. According to this theory the most common case is that, as one goes from element to element, the newly added electron (more correctly one of the electrons present in the completed atom) is fitted into the outermost group. With this addition the outer structure of the atom and therefore the chemistry depending in the first place on this outer structure undergoes a very essential change. The rational use of the quantum theory leads, however, to the result that, although this type is most frequent, a place is bound to come in the successive building up of the atoms from nuclei and electrons where the outer structure remains unchanged and the new incoming electron is fitted into a deeper group. We meet with such cases in groups of elements including the triads of iron, palladium and platinum metals and also the family of the rare earths. Various considerations insistently demand that after lanthanum (12) there must follow a series of elements whose inner groups only are completed by the addition of new electrons. This change in arrangement necessarily causes only a small chemical difference between neighboring elements. It can be seen from the table how, beginning with cerium, the inner lying 4 quantum groups are gradually completed until the number 32 is reached with the element 71 (Lu).

If now we go one step further the next element 72, in contrast to all preceding "rare earths," must differ in its outer structure. This causes a proportionally greater difference between the chemical characteristics of the elements 72 and 71 than those existing between the elements 71 and 70 or any other two members of the group of the rare earths; on the other hand the atomic structure of the element 72 shows an extraordinary similarity to the structure of the 40th element zirconium. The addition of another electron and simultaneously with this the increase by 1 of the number of electrons arranged in the outer group causes the element 72 to be quadrivalent in contrast to the trivalent constituents of Marignac's ytterbium. That the quantum theory of atomic structure requires unconditionally the quadrivalence of the element 72 can be shown by the

Number of electrons contained in the different groups of the neutralized atom

$N \diagdown {}^{n}_{k} \diagdown k$	1_1	$2_1 2_2$	$3_1 3_2 3_3$	$4_1 4_2 4_3 4_4$	$5_1 5_2 5_3 5_4 5_5$	$6_1 6_2 6_3 6_4 6_5 6_6$	$7_1 7_2$
1 H	1						
2 He	2						
3 Li	2	1					
4 Be	2	2					
5 B	2	2 1					
⋮	⋮	⋮					
10 Ne	2	8					
11 Na	2	8	1				
12 Mg	2	8	2				
13 Al	2	8	2 1				
⋮	⋮	⋮	⋮				
18 A	2	8	8				
19 K	2	8	8	1			
20 Ca	2	8	8	2			
21 Sc	2	8	8 1	(2)			
22 Ti	2	8	8 2	(2)			
⋮	⋮	⋮	⋮	·			
29 Cu	2	8	18	1			
30 Zn	2	8	18	2			
31 Ga	2	8	18	2 1			
⋮	2	8	18	⋮			
36 Kr	2	8	18	8			
37 Rb	2	8	18	8	1		
38 Sr	2	8	18	8	2		
39 Y	2	8	18	8 1	(2)		
40 Zr	2	8	18	8 2	(2)		
⋮	⋮	·	·	⋮	⋮		
47 Ag	2	8	18	18	1		
48 Cd	2	8	18	18	2		
49 In	2	8	18	18	2 1		
⋮	⋮	⋮	18	⋮	⋮		
54 X	2	8	18	18	8		
55 Cs	2	8	18	18	8	1	
56 Ba	2	8	18	18	8	2	
57 La	2	8	18	18	8 1	(2)	
58 Ce	2	8	18	18 1	8 1	(2)	
59 Pr	2	8	18	18 2	8 1	(2)	
⋮	⋮	⋮	·	⋮	⋮		
71 Lu	2	8	18	32	8 1	(2)	
72 Hf	2	8	18	32	8 2	(2)	
⋮	⋮	⋮	⋮	⋮	⋮	⋮	

N_k \ n_k	1_1	$2_1 2_2$	$3_1 3_2 3_3$	$4_1 4_2 4_3 4_4$	$5_1 5_2 5_3 5_4 5_5$	$6_1 6_2 6_3 6_4 6_5 6_6$	$7_1 7_2$
79 Au	2	8	18	32	18	1	
80 Hg	2	8	18	32	18	2	
81 Tl	2	8	18	32	18	2 1	
86 Em	2	8	18	32	18	8	
87 –	2	8	18	32	18	8	1
88 Ra	2	8	18	32	18	8	2
89 Ac	2	8	18	32	18	8 1	(2)
90 Th	2	8	18	32		8 2	(2)

help of various considerations of which the following may be easily understood. A trivalency of the element 72 would be equivalent to the condition that in the successive building up of the atom as indicated above the sixty-ninth electron in the element 72 should be bound more strongly than in the element 73. The latter (tantalum) is in fact a quinquivalent element and so the sixty-ninth electron here belongs to the valency electrons. The loosening of the binding of an electron bound in a certain type of orbit in going from one element to the next is not compatible with the demands of quantum theory. This is due to the fact that such a transition is connected with an increase of the nuclear charge and therefore with an increase of the coulomb attractive force which determines the firmness of the binding.

After this unequivocal statement of the theory the discovery of Urbain, according to which Marignac's ytterbium should consist of the three constituent elements 70, 71 and 72, seemed to be a serious obstacle to the quantum theory. It was principally with the object of clearing up this point that induced Dirk Coster and the author to search for the element 72 which, according to the theory should be similar to zirconium.

Elements closely related chemically often accompany each other in minerals. Niobium (columbium) is very often accompanied by tantalum, molybdenum by tungsten, yttrium by holmium and other rare earths and so the immediate thing to do was to look for the missing element 72 in zirconium min-

erals. After the foundation of the X-ray spectroscopy by Moseley and its development in the hands of Siegbahn and his coworkers we have secured an ideal method for the identification of already known or as yet unknown elements and it seemed best to use this method of investigation.

3. The probable abundance of the missing element

It could not be predicted a priori whether the missing element was present in sufficiently large quantities to be recognizable in the minerals which were to be investigated. Yet there were many indications that the missing element was not rare. Elements with even atomic numbers are in general more abundant than those with odd atomic numbers. In the last year this question has been discussed many times by Harkins and others both on the basis of statistical data and in connection with speculations concerning the building up of the atomic nuclei.

These considerations appeared to us to be favorable as did also a comparison of the abundance of the elements Si, Ti, Zr and Th in the crust of the earth. The latter amounts in the lithosphere according to Clark, Washington and Jolly to

	per cent
SiO_2...	59.09
TiO_2.................	1.05
ZrO_2.............	0.04
ThO_2..............	0.002

4. Discovery of hafnium

The investigation of the L-spectrum of the first Norwegian zircon enabled us to recognize at once the presence of two very distinct lines α_1 and α_2. These were situated exactly on the positions interpolated by means of the Moseley law. Shortly afterward the β_1, β_2, β_3 and γ_1 lines were also identified. Furthermore the comparison of intensities of the lines (which is an important control) was fully satisfactory and therefore the presence of not inconsiderable amounts of the element 72 in our mineral seemed to be definitely settled. This did not settle the question of the chemical properties of the element 72 at that time. Its presence in the zirconium mineral could

indeed be purely accessory. The investigation of a great number of various zirconium minerals showed the presence of this new element in variable but in no case inconsiderable amounts in every one of them. We turned then to the commercial zirconium preparations labeled as pure and these also likewise showed the presence of the expected element. The near relationship of the new element to zirconium seemed therefore to be settled. The next problem was to separate the new element from zirconium. With this object we have fused the mineral with acid potassium fluoride and extracted the melt with hot water containing some hydrofluoric acid. Potassium zirconium fluoride is a substance very easily soluble in the hot and only slightly soluble in the cold water and is therefore adapted very well to a systematic crystallization (49). After a few crystallizations we investigated the different fractions. The new element was found to be enriched in the mother liquor while much weaker X-ray lines were emitted by the crystalline residue than by the original material. This same method starting from commercial pure zirconium preparations permitted us to secure rather quickly zirconium oxide which no longer showed the lines characteristic of the new element.

After the identification of the new element by means of X-ray spectroscopy was completely successful and after its presence in all the zirconium minerals and preparations investigated was proven and the partial separation from zirconium was successful, D. Coster and the present writer reported on January 2, 1923, in a letter addressed to *Nature* (16, 17, 18) the discovery of the new element and proposed for the new element the name Hafnium. This name was suggested by Hafnia the Latin name for the city of Copenhagen, in which the investigation was carried out, the work being done at the Institute for Theoretical Physics which is under the direction of Professor Niels Bohr.

5. Earlier search for new elements in zirconium minerals

Since the discovery of zirconium by Klaproth (1789), the discovery of new elements in zirconium minerals has often been

announced.[2]   Thus in 1845 Svanberg expressed the view that zirconium minerals contained an element similar to zirconium, which he called norium.   Sjögren, another Swedish chemist, a few years later, again thought he had found Svanberg's norium in the zirconium mineral catapleiite.   Then came Nylander's announcement (1869) of the discovery of jargonium, an element similar to zirconium, but having a lower atomic weight, and in the same year Church thought he had discovered the new element nigrium.   We may add to this list the announcement of Ogawa (nipponium 1908), and of Hoffmann and Prandtl (1901), who believed they had found a new earth ("euxen earth") in the mineral euxenite.   The genuineness of all these announcements was later disproved by different investigators, including Marignac, Weibull and Hauser, who showed the identity of norium and so on with zirconium.   Most of these announcements were made on the basis of peculiar chemical reactions believed not to be characteristic of zirconium, and from this fact alone we can straightway conclude that the above announcements have nothing to do with the presence of hafnium, as zirconium and hafnium show the same chemical reactions.   Nevertheless, the latter element was without exception undoubtedly present in the investigated samples.

At the time when X-ray spectroscopy was not yet known, the discovery of hafnium could hardly have been made by any other methods than by atomic weight determinations carried out with zirconium preparations of different origin, or by density measurements of these specimens.   Such determinations were repeatedly carried out, but the methods used were (compare section V) not sufficiently accurate to enable the detection of the presence of 1 to 3 per cent hafnium in the preparations of

zirconium investigated. Since the atomic weights of zirconium and hafnium are very appreciably different, it is to be expected that the percentage solubility of a zirconium compound will vary with its hafnium content. This ingenious method of attacking the problem of the possible presence of new elements in zirconium was chosen by Marignac. His failure was due solely to the fact that the technique of solubility measurements was at this time not sufficiently developed, to enable him to find the minute differences in the percentage solubilities of his different fractions.

We shall mention finally the attempt of Hauser to find new elements in zirconium, by investigating the optical spectrum of zirconium samples of different origin. The failure of his efforts was due to the intricate nature of the zirconium spectrum, and furthermore, to the fact that the variation of the intensity of the hafnium lines, which were all rather weak, was insufficient to enable the detection of the presence of a new element in his samples.

II. METHODS FOR SEPARATING HAFNIUM FROM ZIRCONIUM

In view of the great similarity between hafnium and zirconium, it is hardly possible to separate these two elements in a single operation. Methods based on repeated operations have therefore to be applied, from amongst which preference is given to crystallization methods, these being the easiest to carry out. The first condition which a compound used for this purpose has to fulfil is that of stability, viz., the compound must withstand decomposition even after a large number of crystallizations from water. This condition itself greatly restricts the number of the eligible zirconium compounds. Not a single zirconium compound, in which the zirconium atom is found in the cation, can be crystallized from water without decomposition, so that we have to have recourse to those compounds in which the zirconium atom is present in the anion. Owing to the great affinity of fluorine atoms for the electron, the complex zirconium fluoride anions are very stable ones. It was by crystallizing a compound containing such an anion that we were

successful in achieving a complete separation of hafnium from zirconium.

1. Crystallization of the double fluorides

By adding the fluoride of potassium or ammonium to a solution of zirconium fluoride, two types of compounds can be obtained, viz., hexafluorides, K_2ZrF_6; $(NH_4)_2ZrF_6$; and heptafluorides, K_3ZrF_7; $(NH_4)_3ZrF_7$. The heptafluorides of zirconium and hafnium having practically the same solubility (compare section III, page 21), we must crystallize the hexafluorides to obtain a separation. In preparing the double fluorides, it is thus necessary to avoid the addition of more than two molecules of the alkaline fluoride, to avoid the formation of the hepta salt. The solubility of both the potassium and the ammonium salt increases rapidly with the temperature; both crystallize in beautiful crystals, and are very suitable for a systematic crystallization (10, 34, 43). The difference in the molecular solubilities of the potassium salts is slightly greater than that of the ammonium compounds. Nevertheless, we gave preference to the latter compound on account of its much greater solubility, so long as we had to deal with large amounts of material. Starting with 2 kgm. of ammonium zirconium fluoride, containing about 3 per cent of hafnium salt, we obtained, after a great number of crystallizations ten fractions containing 30 to 80 per cent of hafnium. These fractions, the total weight of which amounted to 300 grams, were then converted into the potassium salt. After a few hundred operations, the best fractions of the potassium salt were found to be practically free from zirconium, but they contained an appreciable amount of columbium, the double fluorides of this element being still more soluble than those of hafnium, and thus accumulating in the best fractions. They also contained iron. To purify the hafnium from these and other impurities, we treated the K_2HfF_6 with sulfuric acid, ignited the sulphate obtained, and extracted the K_2SO_4 with hot water. The hafnium oxide was then converted into the neutral sulfate and dissolved in water, this solution being kept for some days at 40°, when a basic salt was precipitated. This

was converted into hafnium hydroxide, dissolved in hydrochloric acid, and the oxychloride thus obtained was crystallized eight times from concentrated hydrochloric acid. The very pure product so obtained was used for the atomic weight determination described on page 17.

2. Crystallization of compounds other than fluorides

Similarly to the stable complex zirconium fluoride anions, complex zirconium oxalate can be obtained. A partial separation of hafnium from zirconium was also achieved by crystallizing the ammonium or the potassium zirconium oxalate (35, 37). Experience gained when carrying out these experiments seems to indicate that here again, as in the case of the double fluorides, compounds with a different content of oxalate exist. Furthermore, basic salts are formed. Only by the crystallization of some of these compounds can a reasonable separation be achieved.

When crystallizing the complex oxalate solution of zirconium hydroxide or zirconium nitrate, a minute concentration of the hafnium in the mother liquor was noted. We also partially separated hafnium from zirconium by crystallizing the double sulfates of potassium and ammonium, though the yield was here, just as in the case of the double carbonates, a rather poor one (37).

A much more successful separation was obtained by crystallizing zirconium oxychloride from about 12 N hydrochloric acid, whilst when less than 9 N acid was used, practically no separation of hafnium from zirconium occurred. In these crystallizations, hafnium is concentrated in the crystals, in contrast with all the above cases. This is of great importance, as all the impurities present concentrate in the mother liquor. When crystallizing the oxychloride in this way from concentrated hydrochloric acid, the elimination of casual impurities takes place simultaneously with a concentration of the hafnium content of the hafnium-zirconium mixture (35, 37).

3. Fractional precipitations

Numerous other methods of separation were tried, the results being more or less satisfactory.

a. *Precipitation with bases.* On fractionally precipitating a solution of zirconium oxychloride with ammonium or other bases, e.g., aniline, the first fractions were found to contain less hafnium than the last ones. The same was the case on precipitating potassium zirconium fluoride with ammonium. We also investigated the separation effected by the hydrolysis of the nitrates, when they were boiled with sodium thiosulfate. These experiments showed that hafnium nitrate hydrolyzed to a somewhat lesser degree than zirconium nitrate (33, 37).

b. *Precipitation with basic chlorides.* An amorphous precipitate of $Zr_2O_3Cl_2 \cdot 3H_2O$ is formed when an alcoholic solution of $ZrOCl_2 \cdot 8H_2O$ is precipitated with ether, acetone and the like. If a solution containing $ZrOCl_2 \cdot 8H_2O + HfOCl_2 \cdot 8H_2O$ is partially precipitated with ether, the first precipitates are poorer in hafnium than the later ones. Moreover, we have obtained hafnium preparations of high concentration in this way (35, 37).

c. *Precipitation with hydrogen peroxide.* Ten grams zirconium sulphate containing 1.5 per cent hafnium sulphate were dissolved in 300 cc. water. The solution was cooled with ice, and then 20 cc. of hydrogen peroxide of 30 per cent concentration, and 60 grams sodium hydroxide dissolved in 250 cc. of water were added. On warming the solution to 50° the hydrogen peroxide gradually decomposed and a precipitate was obtained. The solution was then cooled with ice, and the precipitate filtered off. After standing at room temperature for twenty-four hours, a new precipitate was obtained. On comparing the hafnium content of these two precipitates it was found that the second one contained about 1.5 times more hafnium than the first one, showing that the zirconium peroxide hydrate is less stable than the corresponding hafnium compound (37).

d. *Precipitation with organic acids.* To a very dilute solution of zirconium oxychloride a dilute solution of benzoic acid was gradually added. In this way seven consecutive precipitates

were obtained. The fourth precipitate was found to contain slightly more hafnium than the first one, and the seventh slightly more than the fourth. Basic zirconyl benzoates have been prepared by Venable and Blaylock (59) by adding an aqueous solution of benzoic acid to a solution of zirconyl chloride. No definite compound was formed, but a series of basic zirconyl benzoates representing various degrees of hydrolysis, such as $ZrO(OH)_2·2ZrO(C_6H_5CO_2)_2·6H_2O$ and so on, were secured. Also, by gradually precipitating a dilute solution of zirconium oxychloride with salicylic or tartaric acid, a very slight accumulation of the hafnium content in the last fractions could be ascertained. In the last mentioned cases, especially in that of tartaric acid, it is difficult to secure equal consecutive fractions by adding the acid solution to that of the zirconium compound. At first no precipitation occurs, but later a very copious precipitate is obtained. The precipitated basic tartrates did not settle readily, and had to be whirled in a centrifuge (37).

e. Precipitation with phosphates. A mixture of zirconium and hafnium nitrates dissolved in concentrated nitric acid was precipitated with sodium phosphate in 11 equal fractions. It was found that the *eighth fraction* already contained less than one tenth of the hafnium amount present in the first precipitate (15, 33). It is of interest to note that zirconium was hitherto considered to have the most insoluble phosphate in concentrated acids; this rôle is now taken by hafnium.

From amongst all the precipitation methods, preference is to be given to the precipitation with phosphates. The conversion of the precipitated fractions into soluble compounds always requires, in contrast to the products of crystallization, more or less elaborate work; for this reason we did not carry out a total separation of hafnium from zirconium by the phosphate or any other precipitation method. It was recently suggested (9) to dissolve the phosphate precipitate in hydrofluoric acid and to crystallize the complex compound thus obtained, containing zirconium, phosphorus and fluorine. It is claimed (9) that the latter crystallization, or that of the ammonium or potassium salt of the above mentioned "acid," can be advantageously used to separate hafnium from zirconium.

4. Further methods of separation

The separation of hafnium from zirconium by distillation of their tetrahalides is rendered very inconvenient by the fact that the sublimation temperature of these compounds is lower than their melting point. The tetrachlorides, for example, can only be distilled at a pressure above 10 atmospheres. By sublimation, only an unsatisfactory separation could be obtained (35). It was also proposed to add to the zirconium tetrachloride compounds like phosphorus pentachloride, to lower its melting point (1). This and similar methods would only be practicable if it were possible to obtain a separation by not more than a few operations with their aid. Attempts to separate hafnium from zirconium, based on the different decomposition temperatures of their sulphates, were only partly successful.

By dialyzing a solution containing the nitrates of zirconium and hafnium, the dialysate was found to contain a slightly higher hafnium-zirconium ratio than the original solution. This is presumably due to a somewhat greater tendency of zirconium to hydrolyze, and thus to accumulate in the dialyzer.

III. PROPERTIES OF HAFNIUM

So far it was chiefly endeavored to elucidate the properties of the compounds of hafnium. The only statements available on the properties of metallic hafnium are the following: It has the same crystalline structure as the metallic zirconium. It was found[3] to crystallize in the hexagonal system, the side of the unit triangular prism being 3.32 and its height 5.46. Therefore the atomic volume works out to be 15.7. The metal was prepared by reducing H_2HfF_6 with sodium.

1. Atomic weight

Professor Hönigschmid kindly undertook to determine the atomic weight of hafnium by preparing the tetrabromide and

[3] The determination of the crystal structure was carried out by Dr. Mark in Dahlem.

determining the ratio $\dfrac{HfBr_4.}{4Ag}$ The last preparations supplied by us contained between 0.57 and 0.16 per cent ZrO_2 as revealed by X-ray spectroscopy. The values 177.79, 177.80 and 178.32, 178.33 were found for the atomic weight. Taking into account that the presence of 1 per cent ZrO_2 lowers the atomic weight by 1.4 units, the atomic weight works out in best agreement to be *178.64* to *178.59* (45).

2. Molecular volume of the oxide and double fluoride.

The densities ($d_{20°}$) of ZrO_2 and HfO_2 were determined by the pyknometer method to be 5.73 and 9.68. Taking for the atomic weights of the two elements 91.3 and 178.6 the values 21.50 and 21.76 are obtained for the molecular volumes of the two oxides.

Hassel and Mark (30) determined the crystalline structure of $(NH_4)_3ZrF_7$ and $(NH_4)_3HfF_7$ by using X-ray methods. The volumes of the elementary cubes of the heptafluorides were found by them to be:

$(NH_4)_3ZrF_7$. . . . . 818.2 $Å^3$
$(NH_4)_3HfF_7$. . . . . 830.6 $Å^3$

The elementary cube containing 4 molecules, the molecular volumes of the two compounds are found to be 123.9 and 125.7, showing thus a difference of 1.5 per cent.

3. Solubility of the double fluorides

We determined (37, 41) the solubility of the $(NH)_2HfF_6$; $(NH_4)_3HfF_7$ in K_2HfF_6 and of the corresponding zirconium compounds both in water and in NH_4F solutions. Some data on the solubility of K_2ZrF_6 were already available from earlier researches (49, 50).

a. *Solubility of the ammonium double fluorides.* The results are seen from figures 1, 2 and 3. The first figure shows the change of solubility with temperatures, the second the effect of increasing NH_4F concentration on the solubility of the hepta-fluorides at 20° and in the third one the concentration of the
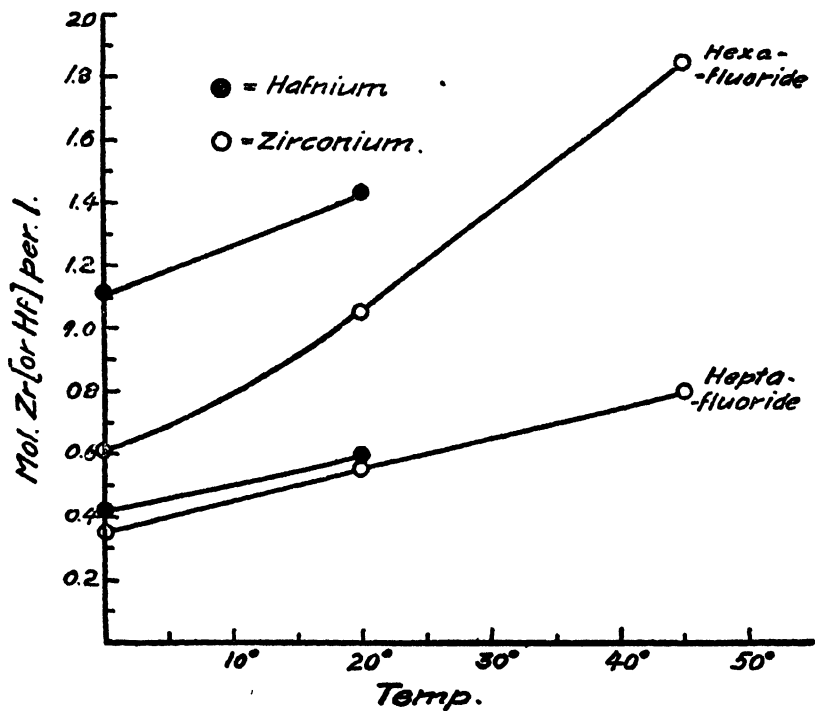
FIG. 1
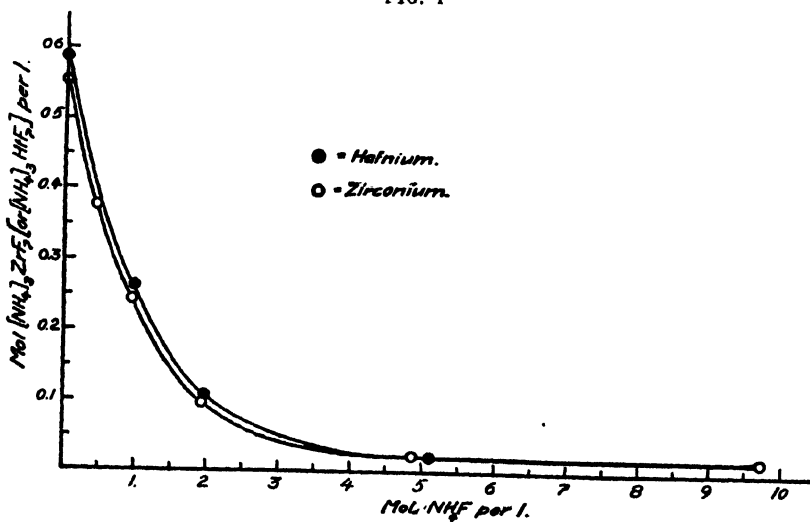
FIG. 2

heptafluorides is plotted on the abscissa and that of the hexa-fluorides on the ordinate.

When determining the solubility of the hexafluoride in a solution of ammonium fluoride the solubility first increases with increasing concentration of the latter due to the formation
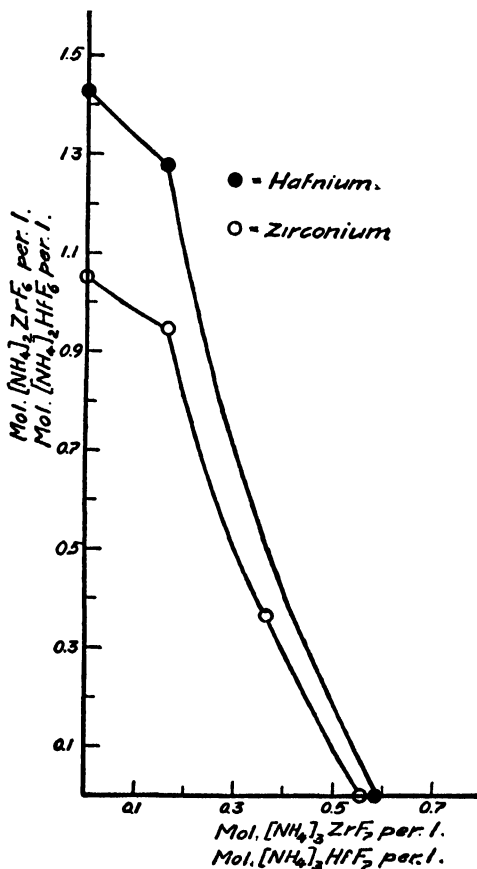
FIG. 3

of heptafluoride. When the concentration of 0.165 mol. NH_4F per liter in the case of the zirconium salt, and of 0.160 mol. per liter in the case of the hafnium salt, is reached the solution is saturated, both as regards the hexa- and heptafluoride. If the ammonium fluoride concentration of the solution is further

increased, the crystal residue of the hexafluoride becomes transformed into heptafluoride. If we still go on, after the transfromation of the whole crystal residue into heptafluoride, to increase the ammonium fluoride concentration of our solution, the solubility of the zirconium or hafnium salt is bound to decrease. It is therefore we find at the point in which the solubility curves of the hexa- and heptafluorides cut each other a maximum solubility for the totality of the salt corresponding to 1.109 mol. zirconium, and 1.439 mol. hafnium per liter, whilst the solubility of the hexafluorides is only 1.050 and 1.425 mol. and that of the heptafluorides only 0.551 and 0.588 mol respectively.

b. *Solubility of the potassium double fluorides.* The molecular solubility of the potassium salts in 1/8 N and 5.89 N HF is seen from the following numbers.

SOLVENT	SOLUBILITY AT 20° OF	
	K_2ZrF_6	K_2HfF_6
1/8 N HF...............................	0.0655	0.1008
5.89 N HF..............................	0.1297	0.1942

The solubility of the potassium hexafluorides of the silicon group is seen from the figures below. The solubility increases when proceeding from silicon to hafnium and diminishes abruptly when proceeding further to thorium.

$t°$	SALT	SOLVENT	SOLUBILITY IN MOL. PER LITER
17.5°	K_2SiF_6	Water	0.00544
20°	K_2TiF_6	1/8 N HF	0.04825
20°	K_2ZrF_6	1/8 N HF	0.06545
20°	K_2HfF_6	1/8 N HF	0.10080
20°	K_2ThF_6	1/8 N HF	"insoluble"

4. Solubility of the oxychloride

The variation of the solubility of the oxychlorides at 20° with increasing hydrochloric acid concentration is shown in figure 4. It is to be observed that with increasing acid concentration the solubility first rapidly and later slowly decreases but

after the concentration of about 9 mol. per liter is attained an increase of the solubility with increasing acid concentration begins. This increase of the solubility is possibly due to the formation of complex compounds such as H_2ZrOCl_4 and H_2HfOCl_4. It is of interest to note that while the solubility of the hafnium salt is practically the same as that of the zirconium salt in hydrochloric acid when the concentration of the latter does not exceed 9 mol. per liter, it is appreciably less soluble in more concentrated hydrochloric acid. When determining the solubility of
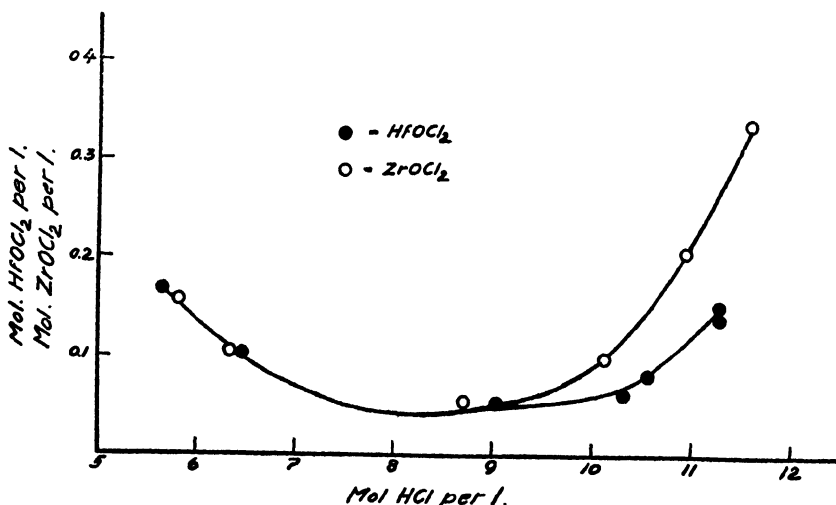
FIG. 4

hafnium oxychloride in still more concentrated acid (11.4 N) a smaller solubility, namely 0.0619, was observed. Further work on this point is in progress.

5. Magnetic susceptibility of the oxide

The following values of the magnetic susceptibilities per gram (X) were found (37)

ZrO$_2$... -0.112×10^{-6}
HfO$_2$... -0.110×10^{-6}

Both oxides are thus diamagnetic.

6. Refractive index

These were determined for (a) the potassium hexafluorides, (b) the potassium and the ammonium heptafluorides and finally (c) for the oxychlorides (37). The following values were obtained.

a. K_2ZrF_6 monoclinic twins...... N (max.) = 1.466; N (min.) = 1.455
K_2HfF_6 monoclinic twins...... N (max.) = 1.461; N (min.) = 1.449

	N	ΔN
b. K_3ZrF_7 regular octahedron...	1.408	0.005
K_3HfF_7 regular octahedron...	1.403	
c. $(NH_4)_3 ZrF_7$ regular octa-hedron....................	1.433	0.007
$(NH_4)_3 HfF_7$ regular octa-hedron....................	1.426	

d. $ZrOCl_2 + 8H_2O$ Needle like
crystals..................... N (ω) = 1.563; N (ϵ) = 1.552
$HfOCl_2 + 8H_2O$ Needle like
crystals..................... N (ω) = 1.557; N (ϵ) = 1.543
Δ N (ω) = 0.006; Δ N (ϵ) = 0.004

7. Optical and X-ray spectra

The optical spectrum of hafnium has been investigated in the region between 7240.9 and 2253.95 A.U. where 760 lines have been measured in the arc and 683 in the spark spectrum (31).

It is of interest to note that several of the strongest hafnium lines are present as weak lines in the zirconium spectrum as measured by earlier investigators (6,23). This was to be expected, because all zirconium minerals and consequently all commercial zirconium preparations contain hafnium.

Detailed investigations on the X-ray spectra were carried out as well. The wave lengths of the principal 16 emission lines of the L-series (14, 51) and 2 lines of the M-series were determined. The K-absorption limit (13) and three L-absorption edges (14, 51) were also observed. From the above data the values for the different levels of the atom were calculated. The reader is referred to page 26 for a fuller discussion of this subject.

IV. METHODS FOR THE DETERMINATION OF THE HAFNIUM CONTENT OF ZIRCONIUM

Any chemical reaction which is characteristic of zirconium can also be used to identify hafnium, as for example, the precipitation of phosphates insoluble in concentrated mineral acids (33), the coloring of tumeric paper, and so on. Recently, different micro-reactions have been tried (52), using both zirconium which was purified from hafnium, and a concentrated hafnium preparation. The reactions tried were: precipitation with potassium dioxalate, with rubidium chloride and ammonium fluoride, with picric acid, with α-nitroso-β-naphthol, but not the slightest difference was found in the two cases.

As hafnium is always found associated with zirconium in nature, and considering the great difficulties which the separation of these elements involves, the practical analytical problem met with in dealing with hafnium is the determination of the hafnium content of zirconium preparations. When such preparations are purified from all impurities, their hafnium content can easily be determined by density measurements, or by the analysis of any well-defined compound, as for instance one of the double fluorides, the sulfate, or one of the tetrahalides. But if impurities are present, the method of quantitative X-ray spectroscopy has to be applied.

1. Density measurements

The oxide of hafnium has a density nearly twice as large as that of zirconium oxide (compare page 33). Density measurements of the oxide thus enable a fairly accurate determination of its hafnium content. The calculation of the latter is based on a standard value of the density of each of the two oxides. As the density varies with the mode of preparation of the oxides, care must be taken that these are always prepared by exactly the same method. In preparing the oxide of zirconium, for example, Venable and Bell[4] (59) ignited the oxychloride, and

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[4] This preparation probably contained about 1 per cent HfO_2 (compare p. 30), whilst Nilson and Pettersson's preparation had presumably a somewhat higher hafnium content.

found a value of 5.49, whilst Nilson and Pettersson (59) found the value of the density of a sample obtained by igniting the sulfate to be 5.85.   This large difference in the densities found is presumably due to the presence of varying amounts of amorphous oxide, which has a lower density than the crystalline compound.   By igniting the preparation at a sufficiently high temperature, or still better by melting it, the whole oxide can be converted into the crystalline state.   Because of the extremely high melting point of zirconium oxide, such a procedure is fraught with very great difficulty, and it was for this reason that we compared the densities of the oxides prepared and treated in exactly the same way.   The normal sulfates were first ignited at a moderate temperature, and then at 1000° for several hours, and their density determined by the pyknometric method.   The hafnium oxide content of the preparation could then be calculated from the density (d) found, according to the formula

$$X = \frac{d - 5.73}{0.0394}$$

The presence of 1 per cent hafnium in a zirconium specimen can still be ascertained by this method.

As with the density of the oxide, so also that of the double fluorides indicates the hafnium content of zirconium.   On account of the larger molecular weight of the double fluorides, this method is less sensitive.   By crystallizing double fluorides, density measurements of such compounds may, however, be of great value.   It is sufficient to remove tiny crystals of, for instance, $(NH_4)_2ZrF_6$ from the different fractions, and to determine their density by the flotation method.   An increase in the hafnium content of the fractions will be at once revealed by the increasing density of the crystals.   Mixtures of methylene iodide and bromoform can be used as the flotation liquid. The density of $(NH_4)_2HfF_6$ being greater than that of methylene iodide, this method cannot be used to determine the density of crystals with a very high hafnium content, though the density of methylene iodide can be increased somewhat by dissolving selenium or other substances of high density in it.

2. Analysis of the double fluoride

The determination of the ratio of the double fluoride to the oxide, or of the former to the ammonia content of the compound also provides us with quick and easy methods for determining the hafnium content of zirconium. For example:

a. Analysis of $(NH_4)_2ZrF_6$. The salt was dried at 60°, weighed, and its ammonia content determined.

The ratio $\dfrac{NH_3}{salt}$ was found to be 0.1149, from which it follows that the preparation contained 73.4 per cent HfO_2 and 26.6 per cent ZrO_2.

b. Analysis of $(NH_4)_3ZrF_7$. The same material analyzed as heptafluoride gave the following values:

$\dfrac{NH_3}{salt}$ = 0.1534, corresponding to 73.5 per cent HfO_2 and 26.5 per cent ZrO_2

$\dfrac{Oxide}{salt}$ = 0.5344, corresponding to 73.6 per cent HfO_2 and 26.4 per cent ZrO_2

The analysis of the K_2ZrF_6 previously used by Marignac to determine the atomic weight of zirconium, can also be used to ascertain the hafnium content of zirconium.

3. Analysis of the sulfate

By determining the ratio of the weights of the sulphate and oxide, the hafnium content of the zirconium sample can easily be calculated. Such determinations (33, 58) can be readily carried out, but no accuracy can be claimed (44).

Concerning the analysis of the tetrachlorides and bromides compare page 29.

4. X-ray spectroscopy

This method is based on the comparison of the intensity of one of the X-ray lines of hafnium with that of a standard substance, mixed in known amount, with the preparation to be investigated. For example, to determine the hafnium content of zirconium oxide we mix a sufficient amount of the oxide of the element 71 to our sample, to ensure that the $L-\beta_2$ line of the

element 71 is as intense as the corresponding hafnium L-β_1 line. The next step is to mix with zirconium oxide free from hafnium suitable amounts of both the elements 71 and 72, so that the above mentioned lines appear with the same intensity. For example, if on the application of a field of 20,000 volts, the latter ratio were found to be 2.5, it follows that the amount of the element 71 which would have to be added to the zirconia to get the 71 L-β_2 line of the same intensity as the 72 L-β_1 would require to be divided by 2.5 to get the hafnium oxide content of the zirconia sample.
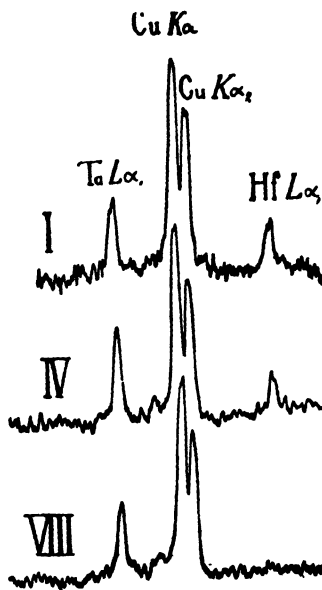
FIG. 5

It is advisable to compare the intensities of two lines lying very close to each other on the photographic plate, in order to diminish the possible error due to different exposure of the different parts of the plate. For this reason we give preference to the comparison of the 71L-β_2 with the 72 L-β_1 line to that of any other two lines, as with our apparatus the distance between these two lines on the photographic plate, using a calcite crystal, amounts only to 0.16 mm. (19, 37).

Instead of determining experimentally the intensity ratio of the two lines, this can be assumed to be unity when strictly corresponding lines of two neighboring elements, e.g. the L-α_1 lines of the elements 72 and 73, are compared (15). This procedure is simpler than that above described, but it is less trustworthy and can lead to erroneous results. It often happens that we do not want to know the absolute amount of hafnium present in zirconium preparations, but only wish to compare the hafnium contents of two samples; in such a case the latter method can be used advantageously. This case arises when we are investigating the effect of a partial crystallization or precipitation on the hafnium content of a zirconium compound. We convert the compound into zirconia, and mix the same amount of tantalum oxide with both samples; the comparison of the intensity ratio of the two lines indicates the effect of crystallization on the hafnium content of the preparation.

The effect of the partial precipitation of zirconium nitrate dissolved in concentrated nitric acid by sodium phosphate is shown in figure 5. This represents a photometric curve of the blackening of the photographic plate, taken with the Moll microphotometer. The copper lines are due to the copper anti-cathode. The original mixture contained about 4 per cent of hafnium oxide; 10 per cent of tantalum oxide was added to each of the different fractions. The figure gives the photometric curves of the first, fourth and eighth fractions. These curves show clearly that the hafnium phosphate is precipitated chiefly with the first fractions, and thus that the phosphate of hafnium is less soluble than that of zirconium.

V. THE ATOMIC WEIGHT OF ZIRCONIUM AND THE HAFNIUM CONTENT OF THE ZIRCONIUM PREPARATIONS USED IN ITS DETERMINATION

The values of the atomic weight of zirconium arrived at by different investigators show very appreciable variations. These variations were due to the unreliability of the methods used, and supply the reason why hafnium was not previously detected on the basis of atomic weight determinations. So far as we can

ascertain, the hafnium content of the samples used in the different investigations, the results of which are shown in the following table, varied between 0.5 and 2 per cent (40, 36).

Values of the atomic weight of zirconium

YEAR	INVESTIGATOR	RATIO	ATOMIC WEIGHT	PER CENT OF HfO$_2$
1825	Berzelius	$Zr(SO_4)_2/ZrO_2$	89.46	2.0 (?)
1844	Hermann	$ZrCl_4/$?	88.64	1.0 (?)
1844	Hermann	$2ZrOCl_2$, 9 $H_2O/$?	89.98	1.0 (?)
1860	Marignac	K_2ZrF_6/K_2SO_4	90.03	0.5
1860	Marignac	K_2ZrF_6/ZrO_2	91.54	0.5
1881	Weibull	$Zr(SO_4)_2/ZrO_2$	89.54	2.0
1881	Weibull	$Zr(SeO_4)_2/ZrO_2$	90.79	2.0
1889	Bailey	$Zr(SO_4)_2/ZrO_2$	90.65	6.0 (??)
1898	Venable	$ZrO\ Cl_2$, $3H_2O/ZrO_2$	90.81	1.0
1917	Venable and Bell	$ZrCl_4/4Ag$	91.76	0.7–1.0
1924	Hönigschmid	$ZrBr_4/4\ Ag$	91.22	0*

* The sample used was purified by us from hafnium by the double fluoride method.

As the presence of 1 per cent HfO$_2$ increases the atomic weight of zirconium by 0.6 unit, the above hafnium contents correspond to errors of from 0.3 to 1.2 units, while the values found differ by as much as 3 units; and even values found by the same investigator, for example, those of Marignac, differ by 1.5 units. We can thus easily understand why the presence of variable amounts of an element of such a high atomic weight as hafnium in the zirconium preparations used could escape detection. It is of interest to note that all the earlier methods gave too low values for the atomic weight (except the second method used by Marignac), but the presence of hafnium fortunately partly compensated the error due to the method. This fact also explains why the atomic weight of zirconium as accepted by the international Committee of Atomic Weights (90.6), differs only by 0.7 unit from the true atomic weight, as quite recently ascertained by Venable and Bell, Hönigschmid, and Aston. Venable and Bell (61) and Hönigschmid (44) used modern and reliable methods, the first two distilling the tetrachloride and determining the ratio ZrCl$_4$/4Ag, while the last-named worker dis-

tilled the tetrabromide and determined the ratio $ZrBr_4/4Ag$. The material used by Hönigschmid was purified from hafnium, and found by us to be free from that element. Through the kindness of Professor Venable we were also able to investigate the hafnium content of the different specimens used by him and Dr. Bell, and we established the presence of 0.7 to 1 per cent of HfO_2 in them (62). Taking into account these results, the atomic weight found by Venable and Bell has to be reduced to an average value of 91.3, or in best accord with the value found by Hönigschmid. Moreover, considering that Aston obtained the value of 91.2 to 91.4 by the positive ray method, the intricate problem of the atomic weight of zirconium may now be regarded as settled.

VI. THE OCCURRENCE OF HAFNIUM IN NATURE

1. The hafnium content of zirconium minerals

In collaboration with Mr. V. Thal Jantzen, the hafnium content of practically every type of zirconium mineral has been determined (39, 37). The chief results of these determinations are seen in the following table, which shows the HfO_2/ZrO_2 ratio of minerals of both nepheline syenitic and of granitic origin.

MINERALS OF NEPHELINE SYENITIC ORIGIN (Products of alkaline residual crystallization)	$\dfrac{HfO_2}{ZrO_2}$	MINERALS OF GRANITIC ORIGIN (Products of silicious residual crystallization)	$\dfrac{HfO_2}{ZrO_2}$
Favas..................	0.007	Naegite...............	0.07
Catapleiite............	0.01	Malacon..............	0.07
Eudialyte.............	0.01	Alvite............ ..	0.11
Elpidite..............	0.01	Cyrtolite.............	0.4
Baddeleyite...........	0.012	Thortveitite.........	0.5
Rosenbuschite.........	0.015		
Eucolite	0.02		
Polymignite...........	0.02		
Wöhlerite.............	0.03		
Zircon.*	0.015	Zircon	0.04

* Zircons are partly products of alkaline and partly of silicious residual crystallization.

It is clearly shown by the above table that while in zirconium minerals that are products of alkaline residual crystallization (25, 27) the HfO_2/ZrO_2 ratio is on the average about 0.015, an appreciably higher ratio—about 0.04—is found in minerals which are products of a less basic, silicious residual magma. Zirconium minerals of granitic origin being far more abundant, the average $\frac{HfO_2}{ZrO_2}$ ratio may work out to be about 0.03. In the primary gaseo-liquid earth material a constant Hf/Zr ratio prevailed. This is most conclusively borne out by the fact that a mixed element, for example chlorine, no matter from what source it may be derived, always contains the same admixture of Cl^{35} and Cl^{37}. This can hardly be accounted for otherwise than by assuming that in the material of the original gaseo-liquid earth, a homogeneous mixture of the two chlorines was present, (viz., that there was a constant ratio $Cl^{35}:Cl^{37}$), and that all the numerous geo-chemical changes which have taken place during and since the solidification of the earth's crust had no influence on this ratio. Zirconium and hafnium being chemically separable, some change was bound to occur in the original Hf/Zr ratio under the influence of the numerous geochemical processes to which this admixture would later be subject. Nevertheless, these changes, consequent on the great chemical similarity of hafnium and zirconium, would be less marked than those occurring in the ratio between tungsten and molybdenum, between tantalum and columbium, between yttrium and the elements of the rare earth group, and very probably in the ratio between any other pair of elements. In the course of the formation of minerals, the original Hf/Zr ratio was altered in favor of zirconium in the products of alkaline residual crystallization, thus leaving behind a zirconium richer in hafnium than in the gaseo-liquid earth. In the products of silicious residual crystallization, on the other hand, we find an appreciable increase of the above ratio. The greatest ratio is found in the case of the minerals alvite (26), cyrtolite and thortveitite, the highest ratio being that for the last mentioned mineral. It is well known, that all zircons exhibit radioactive properties, by virtue of the

presence in them of minute amounts of uranium and thorium. Zircons with a large uranium or thorium content were also found in several cases to contain rather large amounts of hafnium, and the radioactivity of zircons accordingly shows a rough parallelism with their hafnium content. Radioactive measurements may thus prove useful when a search is being made for zircons with a high hafnium content (39, 37).

It is of interest to note that we have not been able to prove the presence of hafnium in any thorium mineral—even though thorium is the higher homologue of hafnium. Neither thorite, thorianite, nor orangite contain hafnium or zirconium. Furthermore, titanium minerals like rutile and ilmenite were found to be free from hafnium (37, 39).

2. The hafnium content of the earth's crust

Clark and Washington estimate the zirconium content of the earth's crust to be about 0.028 per cent. If we take the average hafnium content of zirconium to be 3 per cent, we find the hafnium content of the earth's crust to be 0.001 per cent. The actual hafnium content of the earth's crust is thus about 1/100,000. The above numbers represent the relative abundance of the two elements in the upper layer of the silicate phase, as rocks and minerals, the analysis of which lead to the above data, are only available for this layer. The average zirconium content of the *total* silicate phase must be less than 0.028 per cent and that of hafnium accordingly less than 0.001 per cent, as these elements, just like other lithophilic elements of residual crystallization, e.g., thorium, uranium, columbium and so on, are found comparatively strongly concentrated in the upper (the peripheral) layer of the silicate phase. For the average zirconium or hafnium content of the whole earth material very appreciably smaller numbers result, these elements being typically lithophilic ones, i.e., they are practically only found in the silicate mantle (25). In hardly any other case can the ratio of the abundance of two elements be determined so easily and conclusively as in that of zirconium and hafnium, owing to the great similarity of these two elements.

VII. GENERAL CONCLUSIONS

1. The relationship between hafnium and zirconium, as compared with the similarity between other pairs of elements

The close relationship between hafnium and zirconium is clearly borne out by the chemical and geochemical evidence adduced in the foregoing chapters. In this section we shall compare this relationship with the similarity between other closely related elements belonging to different periods of Mendelejeff's system. Numerical data are available about the following properties, and these we must therefore consider primarily:

a. Molecular volume of the oxides.

b. Solubility. (The ease with which they can be separated by crystallization and the like (degree of basicity).)

c. Refractivity. (Molecular refraction.)

The great similarity between zirconium and hafnium is so firmly established by what has already been said, that only the comparison of their similarity with that existing between the most closely related elements has any immediate interest; for example, the similarity existing between rubidium and caesium, strontium and barium, yttrium and the group of rare earths, columbium and tantalum, molybdenum and tungsten, requires consideration.

a. The density and molecular volume of the oxides of the titanium group is seen from the following table:

	DENSITY	MOLECULAR VOLUME
TiO₂.................................	4.26	18.8
ZrO₂.................................	5.73	21.5
HfO₂.................................	9.68	21.7
ThO₂.................................	10.22	25.8

The molecular volumes of the oxides of titanium and its higher homologues as functions of their atomic numbers are also plotted in figure 6. While we find appreciable differences between the molecular volumes of the oxides of titanium and zirconium, and likewise between those of hafnium and thorium, in the case

of zirconium and hafnium, corresponding to the change from 42 to 72 in the atomic number, we only find a change of about 1 per cent in the molecular volumes. Appreciably greater values are found for the difference in the molecular volumes of the oxides of yttrium and most of the rare earth metals, or of columbium and tantalum. The close relationship between hafnium and zirconium, compared with that of zirconium and titanium on one side and hafnium and thorium on the other is far from being an unique phenomenon in the periodic table. We find for instance similar
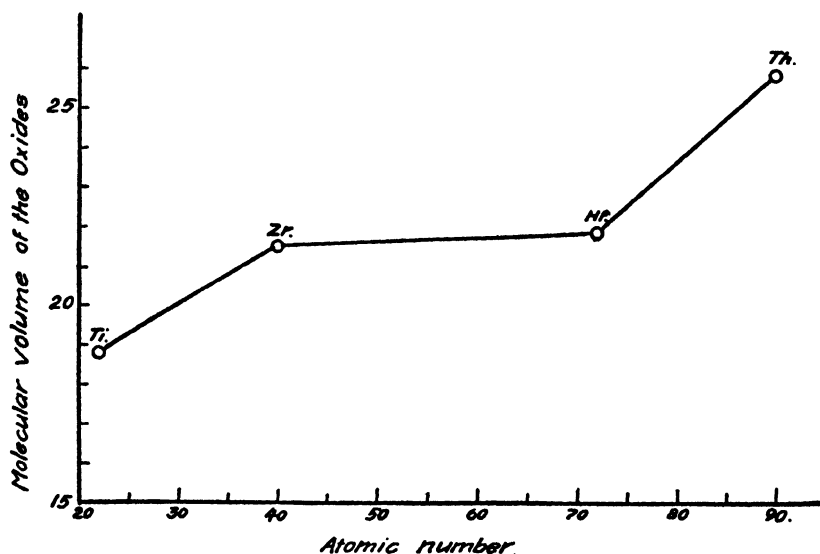
FIG. 6

regularities in the third, fifth and sixth vertical rows of Mendelejeff's system. Molybdenum and tungsten are much more similar than chromium and molybdenum, or tungsten and uranium. Of 49 analyses of vanadium minerals in Doelter's "Handbuch," we find none indicating columbium; of 211 analyses of titanium minerals zirconium is present in only ten cases, while the corresponding members of the fourth and fifth periods are found in most cases associated in nature (25, 37).

b. The close relationship between hafnium and zirconium is best shown by the small differences in the solubilities of cor-

responding compounds. Even in the case of the potassium double fluorides the ratio of the solubilities of the corresponding compounds amounts only to 1.6. Much greater differences were found between the solubilities of K_2CbF_7 and K_2TaF_7 (in 5 N HF), for which a ratio of 5 was determined, and a ten times greater value was found between the solubilities of the fluorides (oxyfluorides) of these elements in an excess of potassium fluoride. The separation of tantalum from columbium, which, like that of hafnium from zirconium, can best be carried out by crystallization of the double fluorides, is in itself a difficult task, and we can only expect to get a separation of hafnium from zirconium after a very large number of crystallizations. In full accordance with this conclusion, we also found that geochemical processes, chiefly governed by the prevailing differences in basicity and solubility, influenced the original zirconium/ hafnium ratio of the gaseo-liquid earth material much less than they influenced the molybdenum/tungsten, the columbium/ tantalum, and even the yttrium/rare earth ratios. No zirconium is found in nature without hafnium, and no hafnium without very appreciable amounts of zirconium, whereas we know several tungsten and tantalum minerals, and several cases in which the original yttrium/rare earth ratio underwent very pronounced alterations (27).

c. The comparison of the refractive index (or of the molecular refraction) of corresponding compounds is also suitable for the comparison of the chemical similarity between two pairs of elements, in that it can be measured with great exactness, and because a very small amount is sufficient for the measurement.

In the four cases investigated (compare page 23), the refractive index of the hafnium salt was found to be very slightly less than that of the corresponding zirconium compound. The difference is in all cases much smaller than that between the refractive indices of such related compounds as the sulphates of rubidium and caesium, of strontium and barium, the potassium fluorides of columbium and tantalum (28), the molybdates, and tungstates of lead and the potassium cyanides of ruthenium and osmium. However, we find similar small differences be-

tween the refractive indices of yttrium and the corresponding compounds of the rare earth elements.

Owing to lack of data, it is difficult to compare the similarity between zirconium and hafnium with that between two neighboring elements of the rare earth group, e.g., between the closely related elements 70 and 71; but we may conclude with certainty
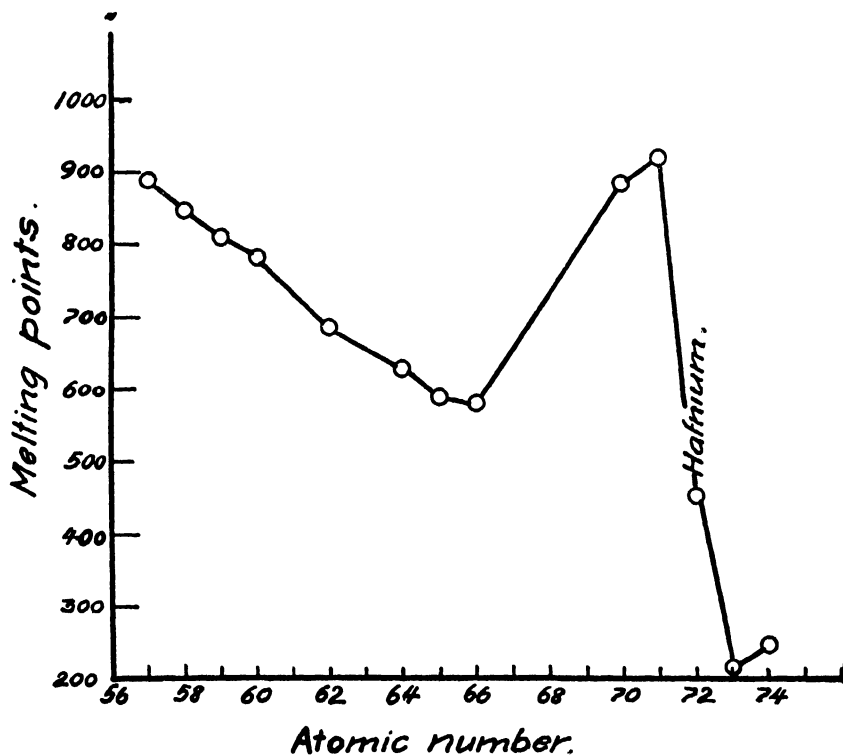
FIG. 7

from the chemical and geochemical data discussed in the foregoing chapters that hafnium and zirconium are more closely related than any other two elements belonging to different periods. The chemical similarity between two corresponding elements of the fourth and fifth series of the periodic system, namely, between rubidium and caesium, strontium and barium, yttrium and the rare earths, zirconium and hafnium, increases

in the order given, and reaches a maximum similarity in the last case. Columbium and tantalum are very closely related chemically, but not in as high a degree as the last-mentioned elements, and this applies still more to the case of the relationship between molybdenum and tungsten.

2. The properties of hafnium as compared with those of the other elements of the fifth period

In figure 7, the melting points of the chlorides of the elements between caesium and tungsten are plotted against the atomic number of their metallic constituent. The curve shows that while the melting point fluctuates between 920° and 588° in the long interval between the elements 55 and 71, a sudden drop amounting to 500° takes place when we pass from the element 71 to the element 72, and this clearly indicates the very great change which ensues in the course of the successive building up of atoms (compare page 6), when one more electron is added to a configuration containing 71 electrons, which represents the last member of the rare earth group. The reason why we consider only the melting points of the chlorides is that only for these compounds are numerical data available for practically every member of the fifth period. But also when we compare any of the chemical properties of the elements of this period, a very abrupt change will be found when we pass from the element 71 to the element 72. Similar very large differences are found between the boiling points of the elements 55–71 and that of 72. The solutions of the chlorides of the elements 55 to 71 show no signs of hydrolysis the solution of the chloride of the element 71 is neutral towards methyl orange (11), but the chloride of hafnium hydrolyzes at once to a very high degree when it comes into contact with water. The normal sulfates of the elements 55 to 71 can only be decomposed by prolonged heating at very high temperatures, whereas the sulphate of hafnium loses appreciable amounts of sulphuric acid even at 500°.

But the conspicuous change in the constitution of the atom after the completion of the inner groups of electrons which takes place with the last rare earth in most beautifully shown

when we consider the energy levels calculated from X-ray data (51). These are shown in figure 8, in which the energy terms of different levels are plotted against the atomic number of the elements of the fifth period. The emphasized features
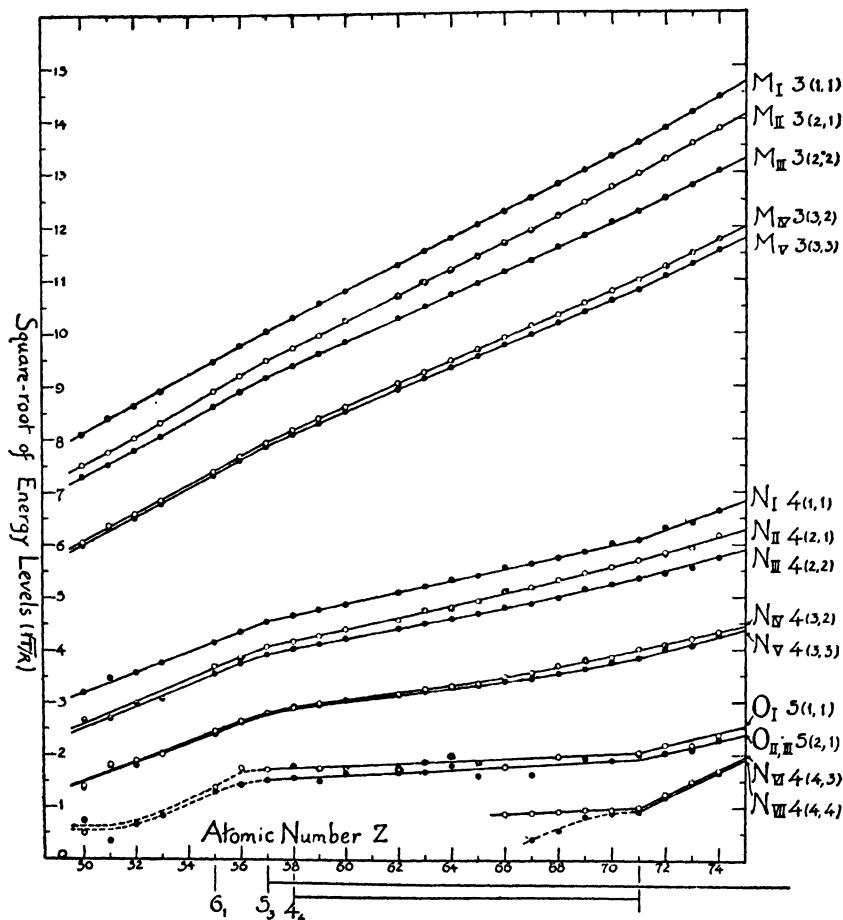
FIG. 8

are most distinctly shown in the curves relating to the levels N_{VI}, N_{VII}, O_I and $O_{II, III}$, where sharp bends occur at the element 71, showing the termination of the rare earth group in a remarkable manner.

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THE ORGANIC COMPOUNDS OF LEAD

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INTRODUCTION

The chemistry of organo-metallic compounds was studied as early as the middle of the last century, but it has been developed extensively only in more recent years. Scientists have realized how much valuable data could be obtained from a study of compounds in which the metals show properties so different from those of their inorganic salts. For instance, medical science has urged the preparation of compounds in the form of which arsenic and mercury could be used for pharmaceutical purposes.

So many articles and books have been published on the subject that it is reasonable to assume that the reader is familiar with the general chemistry of organo-metallic compounds. The organic compounds of lead resemble in structure, stability and reactions those of tin and silicon. The stable valency of lead in its organic compounds is 4. The tetra alkyl compounds, such as $Pb(CH_3)_4$, are colorless heavy liquids, insoluble in water and miscible with organic solvents. They withstand temperatures up to 140°C., and do not react with dilute acids or alkalis. The action of halogens or strong acids replaces one or two of their organic groups by acid radicals:

$$Pb(CH_3)_4 + 2Br_2 = Pb(CH_3)_2Br_2 + 2CH_3Br$$
$$Pb(CH_3)_4 + CCl_3 \cdot COOH = CCl_3COOPb(CH_3)_3 + CH_4$$
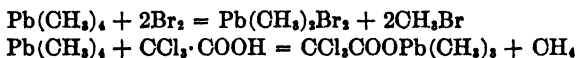
The new compounds so obtained, the di and tri alkyl lead salts, are white solids, crystallizable and soluble in water and in organic solvents. Their aqueous solutions give the characteristic reactions of their anions, while the organic lead radicals show properties similar, for the $PbAlK_3^+$, to alkaline metals and for the $PbAlK_2^{++}$ to the zinc ion. The aryl compounds are similar in

43

their properties to the alkyl derivatives, but are, in general, more stable and less soluble; the tetra aryl lead compounds are solids instead of liquids.

A few compounds are known corresponding to the types PbR_2 and PbR_3 or Pb_2R_6. They are unstable and tend to revert to PbR_4 compounds under deposition of metallic lead.

The first reference to organic lead compounds was by Löwig (1) in 1852: "I have prepared the compounds which Pb and Sn form with the ethyl group. . . . . They are obtained by interaction of ethyl iodide and sodium alloys." About the same time, Cahours (2) reported that some organic lead compound is formed when metallic lead is heated with ethyl iodide. Lowig (3) then published his complete work, in which he describes the method of preparation of an ethyl lead compound and of triethyl lead salts.

His method consisted in the interaction of lead sodium alloys with ethyl iodide; the product obtained was a heavy liquid, fairly stable, and containing only the elements Pb, C and H. However, he was unable to purify it and assigned to it the formula $Pb(C_2H_5)_3$. Exposed to the air, it went over to a white crystalline compound which proved to be tri ethyl lead carbonate $[Pb(C_2H_5)_3]_2 CO_3$. From this, by the action of acids, he obtained other salts in which the triethyl lead radical acts as a monovalent metal, giving $Pb(C_2H_5)_3Cl$, $[Pb(C_2H_5)_3]_2SO_4$.

In 1859 G. B. Buckton (4) showed that alkyl lead compounds could be prepared by double decomposition between diethyl zinc and lead chloride, according to the reaction:

$$2Zn(C_2H_5)_2 + 2PbCl_2 = 2ZnCl_2 + Pb + Pb(C_2H_5)_4$$
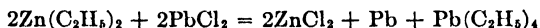
He explained that the product obtained by Löwig was probably impure $Pb(C_2H_5)_4$, and shows that this can be converted into triethyl lead salt by the action of acids:

$$Pb(C_2H_5)_4 + HCl = Pb(C_2H_5)_3Cl + C_2H_6$$
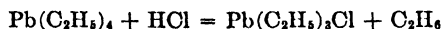
Later, Klippel (5), Frankland and Lawrence (6), Polis (7), Ghira (8) and Werner and Pfeiffer (9) studied the compounds they prepared by the lead sodium or ethyl zinc reactions.

In 1904, an important contribution was made by Pfeiffer and Truskier (10) who showed that tetraphenyl lead could be prepared from a Grignard reagent:

$$4C_6H_5MgBr + 2PbCl_2 = Pb + Pb(C_6H_5)_4 + 2MgBr_2 + 2MgCl_2$$
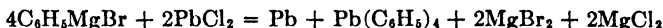
Another new method of preparation was contributed in 1907 by Tafel's discovery (11) that in the electrolytic reduction at a lead cathode of acetone dissolved in sulphuric acid, some di- or tetra-*iso*propyl lead is formed. By direct action of bromine on these products, he obtained tri-*iso*propyl lead bromide, and also a compound of a new type, di-*iso*propyl lead dibromide $Pb(C_3H_7)_2Br_2$. Not much attention was paid after that to organic lead compounds until 1916, when Grüttner and Krause (12) and later Krause (33) and his co-workers commenced an exhaustive study of alkyl and aryl lead compounds and their derivatives. Their main objective was, at first, to obtain optically active lead compounds, but although they do not report the separation of optically active compounds, their results extend far beyond this. They used Pfeiffer's method to prepare their compounds, and showed that tri-alkyl (or aryl) lead halides, and di-alkyl (aryl) lead di-halides could be made to react with Grignard reagents to give compounds containing different organic radicals (12).

$$Pb(CH_3)_3Br + C_2H_5MgBr = Pb(CH_3)_3C_2H_5 + MgBr_2$$
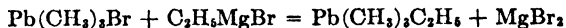
This resulted in the systematic preparation of compounds containing 2, 3 and 4 different organic radicals, and the corresponding salts.

In 1919, Krause prepared a compound containing tri-valent lead, $Pb(C_6H_4 \cdot CH_3)_3$ (13), and in 1922, a divalent organic lead compound, $Pb(C_6H_5)_2$ (14). Finally, an unsaturated alkyl lead compound was isolated by T. Midgley, Jr. (15).

This survey covers the main developments of our knowledge of the chemistry of organic lead compounds. No practical application had been found, nor perhaps thought of, for any of them until the recent discovery of T. Midgley, Jr., and T. A. Boyd, that the presence of a small amount of tetraethyl lead in

gasoline would prevent detonation in internal combustion engines (16). The preparation of this compound on a large scale has resulted, and its wide use will probably further increase the interest of chemists in the organic compounds of lead.

Unlike other metals, lead does not directly form compounds in which the metal is linked to organic groups and a halogen, as is the case with magnesium, for instance. Such compounds must always be formed indirectly from a compound in which all the valencies of the lead are occupied by hydrocarbon radicals. This accounts perhaps for the fact that most of the methods of preparation of organic lead compounds are different from those used with other metals.

1. Preparation from organic halides

a. Reaction of metallic lead with alkyl iodides. Mention is made by Cahours (2) of the fact that metallic lead is attacked by ethyl iodide, but the amount of product is probably small, as the experimenter was unable to isolate the product, as in the case of mercury and tin. This can probably be accounted for by the fact that the product is not an alkyl lead halide, similar to CH_3HgI, for instance, but a true alkyl compound such as $Pb(C_2H_5)_4$. Indeed, when some reagent is added which will take up the halogen set free, the reaction proceeds smoothly and gives good yields. Suitable reagents for this purpose are, for instance, powdered aluminum, zinc, or silicon with concentrated sodium hydroxide solutions (17). The reaction can probably be written as follows:

$$Pb + 4C_2H_5I + 2Zn + 8NaOH = Pb(C_2H_5)_4 + 4\,NaI + 2Zn(ONa)_2 + 4H_2O$$
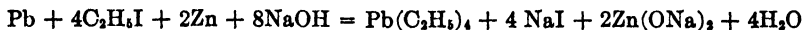
Reactions of this type have apparently been studied only in the case of ethyl iodide. They would probably be much less successful with bromides or chlorides, either aliphatic or aromatic.

b. Reactions of lead sodium alloys with organic halides. This method was originated by Löwig (3) as an extension of his method

of preparation of other organo-metallic compounds. In this reaction the organic halide is merely poured onto finely divided lead sodium alloy contained in a flask equipped with a reflux condenser, and the reaction can be written:

$$PbNa_4 + 4C_2H_5I = Pb(C_2H_5)_4 + 4NaI$$

the products obtained being tetra-alkyl or aryl lead compounds and sodium halides. Löwig and Klippel (5) used ethyl iodide with lead sodium alloys varying from 16 to 25 per cent Na. They reported a vigorous reaction, and the formation of a compound which they believed to be $PbEt_3$ or Pb_2Et_6. In one instance, Löwig amalgamated his lead and sodium with a large excess of mercury. This produced a smooth reaction and gave a good yield of alkyl lead compound, but no mercury compound was formed. Polis (7) used the same reaction on brombenzene, but added a small amount of ethyl acetate to promote the reaction. No satisfactory explanation has been given, however, for the mechanism of the reaction. Ghira (8) states that, if one follows exactly the procedure given by Löwig, no reaction takes place, but that the addition of a small amount of water makes it proceed smoothly, and that, when ethyl iodide is used, the product obtained is $Pb(C_2H_5)_4$ and not $Pb(C_2H_5)_3$.

It seems established, therefore, that no reaction takes place, at least at room temperature, between pure lead sodium alloys and organic halides. The rôle played by the water or the ethyl acetate is not well understood. The remark can be made, however, that zinc plus sodium hydroxide and sodium plus water or an ester are alike in that they both are slow generators of nascent hydrogen, and the process might thus well be considered to be one of reduction.

A similar method has been developed by the General Motor Research Corporation for the preparation of organic lead compounds. This method, which is equally suitable for use with alkyl and aryl bromides and chlorides as well as iodides, is used for the preparation of tetraethyl lead on a commercial scale and is somewhat as follows (17):

In a reacting vessel equipped with a suitable stirring device

and a reflux condenser, one molecule of ground lead sodium alloy, $PbNa_4$, is poured into four molecules of ethyl bromide to which 0.4 mole of pyridine has been added. Water is then added slowly, under constant stirring. Some hydrogen is evolved, together with butane, the sodium is converted into sodium bromide and most of the ethyl groups go to form tetraethyl lead. Presumably, diethyl lead is formed as an intermediate product, which finally breaks down to metallic lead and tetraethyl lead. The reaction is controlled by the rate of addition of the water and the rate of cooling of the reacting mass. Much heat is evolved in the process and the temperature must be kept around the boiling point of the alkyl halide in order to avoid excessive evaporation losses.

When all the sodium is used up, as indicated by the fact that no reaction takes place on addition of water, enough water is added to render the mass fluid, and it is subjected to a steam distillation. The alkyl halide, if present in excess, distills first, and then the lead tetraethyl, the condensate being tetraethyl lead and water in the ratio 1 to 4 by volume. The product is then washed free from pyridine and filtered or settled to separate a small amount of water kept in suspension.

The pyridine, which can be replaced by an amine, triethylamine or dimethylaniline for instance, plays an important, though little understood, part in the mechanism of the reaction. It probably promotes the reactivity of the alkyl halide molecule by the intermediate formation of an addition compound:

$$C_6H_5N(CH_3)_2 + C_2H_5I \longrightarrow$$

$$C_6H_5 \diagdown \diagup CH_3 \longrightarrow$$
$$N$$
$$C_2H_5 \diagup \vert \diagdown CH_3$$
$$I$$

$$C_6H_5N \diagup^{CH_3}_{\diagdown CH_3} + C_2H_5 - + I -$$
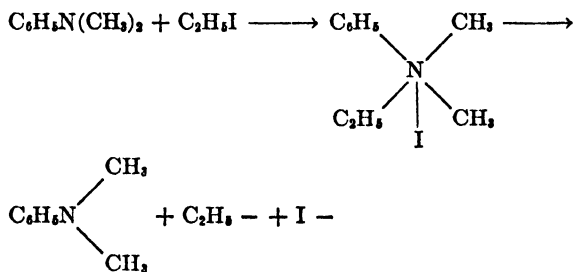
In all cases, the catalyst is recovered unchanged at the end of the reaction.

2. Preparation by double decomposition with other organo-metallic compounds

a. From di-ethyl zinc and lead chloride. This reaction was originated by Buckton (4) and used later on by Frankland and Lawrence (6). Lead chloride is added slowly to diethyl zinc, and tetraethyl lead is formed, while zinc chloride and metallic lead separate:

$$2Zn(C_2H_5)_2 + 2PbCl_2 = Pb + Pb(C_2H_5)_4 + 2ZnCl_2$$

b. From Grignard reagents.

$$4C_6H_5MgBr + 2PbCl_2 = Pb + Pb(C_6H_5)_4 + 2MgBr_2 + 2MgCl_2$$
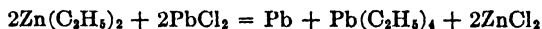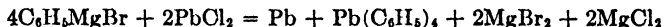
This reaction was first reported by Pfeiffer and Truskier (10). It presents no difficulty, gives high yields and is probably the best method to use on a laboratory scale. It also lends itself to the preparation of compounds in which the lead is linked to different groups:

$$C_2H_5MgBr + Pb(CH_3)_3Br = Pb(CH_3)_3C_2H_5 + MgBr_2$$
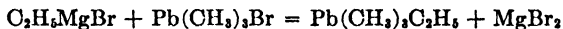
Here again, however, the mechanism of the reaction is not fully understood, the equations only summing up the results.

Indeed, according to the above, one would expect the reaction to be complete without the usual hydrolysis of the Grignard complex with water. However, after long interaction, the mixture still reacts vigorously with water, and it is only after the hydrolysis that the final lead compound can be extracted. One must thus admit the formation of an intermediate addition compound, probably containing ether, and which is decomposed by water to give the final products of the reaction.

3. Electrolytic reduction

J. Tafel (11) in 1907 reported that a lead cathode used in electrolyzing acetone dissolved in aqueous sulphuric acid was constantly losing weight. He studied the reaction further with G. Renger (19) and found it to be caused by the formation of either di- or tetra-*iso*propyl lead. The yields are far from being quanti-

tative, either on the current or on the acetone used, as many other reduction products are formed at the same time. The method is, however, worth while mentioning, as it illustrates once more the formation or organic lead compounds by a process of reduction.

The important general reactions of organic lead compounds have been suggested in the introduction. They will be studied here somewhat more in detail, under headings indicating the type of reagent considered.

1. Stability

In general, the saturated organic lead compounds are quite stable when pure and are little influenced by air, moisture, moderate heating or light. Long exposure to sunlight, however, or heating at a temperature varying with the compounds considered, results in decomposition, with separation of metallic lead.

The tetra alkyl and aryl lead compounds vary in stability with the nature of the organic radicals they contain. In the aliphatic series, the stability decreases with increasing molecular weight; also, secondary alkyl groups give the compounds a much lower stability than the corresponding primary groups. This is probably due to steric hindrance, as the presence of a tertiary carbon atom not directly bound to the lead atom has no effect on stability. Thus, tetra-methyl lead, $Pb(CH_3)_4$, is the most stable compound in the alkyl series; tetra-n. propyl lead is more stable than tetra-sec. propyl lead, whereas the difference between tetra-n. and tetra-isobutyl lead is much less marked.

In the aryl series, little difference is shown by the various compounds. This is not surprising, for the nature of the Pb-C linkage is hardly affected by further substitutions in the benzene nucleus.

In the few compounds in which the lead is not truly tetravalent, such as $Pb(C_6H_5)_3$, $Pb_2(C_2H_5)_6$, $Pb(C_6H_5)_2$, the stability is much lower. The di-lead hexa alkyl and the di-aryl lead compounds absorb oxygen and are easily decomposed by heat, the former

being even slowly decomposed by diffused light into metallic lead and lead tetraethyl.

The organo-plumbic salts are more stable, perhaps, than the saturated alkyl and aryl compounds. They are, in general, not hydrolyzed and some can be recrystallized and melted without decomposition. The compounds of the general type PbR_3X are more stable than the PbR_2X_2 compounds. The latter, in some cases, tend to decompose into hydrocarbons and an inorganic lead salt, as they contain all the elements of the latter with, in addition, the two organic groups.

Compounds in which three of the valencies of lead are satisfied by inorganic radicals, the fourth one alone being a Pb-C linkage, are unknown and, if formed at all, would probably break down instantaneously. This is easily understood when one keeps in mind that lead is respectively di- and tetra-valent in its stable inorganic and organic compounds. For the compounds of tetra-valent lead, the stability will thus decrease with increasing number of inorganic groups.

2. Reaction with acids

The linkage between lead and carbon is stable to dilute acids, but is broken by concentrated strong acids or by weaker acids on heating. For instance, a 1:1 by volume mixture of H_2SO_4 and H_2O does not attack tetraethyl lead at room temperature. On gentle heating the same acid will react to form tri-ethyl lead sulfate and ethane.

$$2Pb(C_2H_5)_4 + H_2SO_4 = [Pb(C_2H_5)_3]_2SO_4 + 2C_2H_6$$
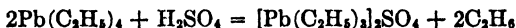
With still stronger acids, such as fuming nitric or 98 per cent sulfuric acid, all organic lead compounds are completely destroyed, the organic matter is partly or completely burnt, and the lead converted quantitatively into nitrate or sulfate.

3. Reactions with alkalis

Dilute and even concentrated alkalis are without effect on tetra-alkyl or -aryl lead compounds. The organo-lead salts

react with alkalis as other salts would. The corresponding hydroxides can be obtained by double decomposition:

$$Pb(CH_3)_3Cl + NaOH = Pb(CH_3)_3OH + NaCl$$
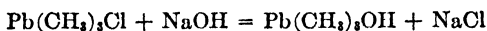
and are soluble in an excess of alkali:

$$Pb(CH_3)_3OH + NaOH = Pb(CH_3)_3ONa + H_2O$$
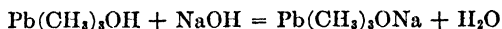
Heating of organic lead compounds with concentrated alkali at high temperatures would probably result in a breaking down of the compound, but no specific data are available on the subject.

4. Action of halogens

The halogens react readily with the lead compounds containing three or four organic groups. At room temperature and with an excess of halogen, they form di-substituted derivatives:

$$Pb(C_6H_5)_4 + 2Br_2 = Pb(C_6H_5)_2Br_2 + 2C_6H_5Br$$
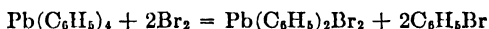
At lower temperature, it is possible to restrain the reaction to the production of mono-substituted derivatives:

$$Pb(C_2H_5)_4 + Cl_2 = Pb(C_2H_5)_3Cl + C_2H_5Cl$$

Thus, Grüttner and Krause (20) have constantly used that method to prepare the various derivatives. The action of bromine at $-70°C.$ gives tri-alkyl lead derivatives; at $-25°C.$ the di-substituted compounds. It is also worth mentioning that, in compounds containing different organic radicals, the halogen exerts a very decided selective action, reacting almost invariably with one of the groups of which there is the larger number. Thus:

$$Pb(CH_3)_3C_2H_5 + Br_2 = Pb(CH_3)_2(C_2H_5)Br + CH_3Br$$
$$Pb(C_3H_7)_3C_2H_5 + Br_2 = Pb(C_3H_7)_2(C_2H_5)Br + C_3H_7Br$$
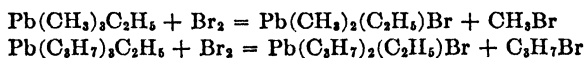
Never does the action of halogen affect another part of the molecule than the Pb-C linkage.

The unsaturated alkyl lead compounds react readily with halogens without elimination of organic halides:

$$Pb(C_6H_5)_2 + Br_2 = Pb(C_6H_5)_2Br_2$$
$$Pb_2(C_2H_5)_6 + Br_2 = 2Pb(C_2H_5)_3Br$$
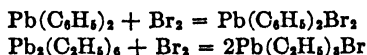
5. Miscellaneous reactions

Metallic sodium reacts with alkyl lead compounds (21) according to the equation:

$$Pb(C_2H_5)_4 + 4Na = Pb + 4NaC_2H_5$$
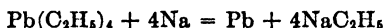
but the reaction is not quantitative, as when Zn or Hg compounds are used, and no pure NaC_2H_5 is obtained.

No reactions are reported between organic lead compounds and other elements.

Mercury, bismuth, thallium and arsenic halides react somewhat like halogens, converting $Pb(C_2H_5)_4$, for instance, into $Pb(C_2H_5)_3Cl$ (12) (22).

TETRA ALKYL LEAD COMPOUNDS

An extensive study of these compounds has been made by G. Grüttner, E. Krause and their co-workers.

Without exception, all tetra-alkyl lead compounds are colorless liquids, heavier than water, having a rather pleasant odor of fruit. They distill undecomposed under reduced pressure, the lower members of the series even under atmospheric pressure. They form explosive mixtures with air, and burn with a characteristic livid blue flame, giving a heavy yellow smoke of PbO.

The stability of the compounds towards atmospheric oxygen and other reagents differs greatly with the nature of the Pb-C linkage. When the carbon atom, linked to the lead is primary, the compound is stable in air and little affected by light. With a secondary hydrocarbon group, the compound is slowly attacked by air, giving yellowish white precipitates of tri-alkyl lead oxides or carbonates. No lead compound containing a tertiary hydrocarbon group has been prepared. All the attempts have resulted only in a reduction with deposition of metallic lead. This difference is also indicated by the atomic refraction of the lead atom, the value of which is always exalted when a primary carbon is replaced by a secondary group. Molecular weight determinations made by freezing point lowering of benzene solutions show that all these compounds exist as single molecules.

Methods of preparation

The two older methods of preparation of these compounds, namely, the interaction of lead-sodium alloys with alkyl iodides, and the reaction of lead chloride on diethyl zinc, are not to be recommended. They are expensive and give only low yields.

Pfeiffer's method, the decomposition of a Grignard reagent with lead chloride, is much easier and less expensive to use in the laboratory. The reaction cannot, however, be applied without modification to the preparation of all tetra-alkyl lead compounds. It is possible to prepare organic compounds of tetravalent lead directly from lead dichloride. The reaction takes place according to the equation:

$$2PbCl_2 + 4C_2H_5MgBr = Pb + Pb(C_2H_5)_4 + 2MgCl_2 + 2MgBr_2$$
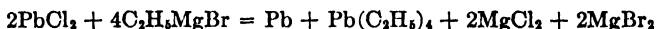
This proceeds quite easily with methyl magnesium chloride, and pure tetramethyl lead can readily be prepared in that way.

When the heavier ethyl magnesium bromide is used, some anomalies are noticeable. After decomposition of the magnesium compound with water, the ether extract is no longer colorless, as was true with tetramethyl lead, but is greenish-yellow and does not contain pure tetraethyl lead. After short exposure to the air, it becomes turbid, and a yellowish-white precipitate separates out, which contains Pb, C and H, and which, upon treatment with acids, gives off CO_2. This is by all evidence an ethyl lead carbonate. After evaporation of the ether a heavy liquid is left which, distilled in an atmosphere of CO_2 under 20 mm. pressure, decomposes when the bath reaches a temperature of 80°C. Metallic lead separates out, first in the vapor, then in the liquid phase. At a slightly higher temperature, a colorless liquid distills over in a temperature range of a few degrees, while metallic lead is separated and gas given off continually. The distillate still shows, though to a lesser degree, the same instability as the ether solution. If the temperature of the bath is raised to 135°C. a mild explosion takes place in the flask, and a cloud of lead is given off. On repeating the distillation, the same decomposition takes place, though it decreases in intensity, and ceases after three or four distillations. The distillate is then colorless, stable

in air, and distills without decomposition under 20 mm. pressure. This proves to be pure lead tetraethyl.

The product obtained from propyl magnesium chloride shows the same properties to an even greater extent.

Such properties cannot be attributed to tetra alkyl lead compounds as these will, when pure, withstand a temperature of 140°C. They recall rather the properties described for unsaturated lead compounds which, as will be seen later, tend to decompose even at room temperature with liberation of metallic lead. Also, the greenish yellow color of the products obtained in this reaction is the same as is shown by $Pb_2(C_2H_5)_6$, or by the crude product obtained by the lead sodium reaction. Such compounds must thus be present in the product of the Grignard reaction, and since their stability increases with increasing molecular weight of the alkyl groups, the method must be modified when it is desired to prepare pure tetra alkyl lead compounds.

Unsaturated alkyl lead compounds add halogen to form di- and tri-alkyl lead halides, in which the lead is tetravalent. A further interaction of these products with a Grignard reagent will then give a tetra alkyl compound, without the loss in yield which is the disadvantage of the distillation method.

This can be represented by the scheme:

$$PbCl_2 \xrightarrow{C_2H_5MgBr} \Big\langle \begin{array}{c} \nearrow Pb(C_2H_5)_4 \searrow \\ \searrow Pb_2(C_2H_5)_6 \nearrow \end{array} \Big\rangle \xrightarrow{Br_2} Pb(C_2H_5)_3Br \text{———}$$

$$\xrightarrow{C_2H_5MgBr} Pb(C_2H_5)_4$$
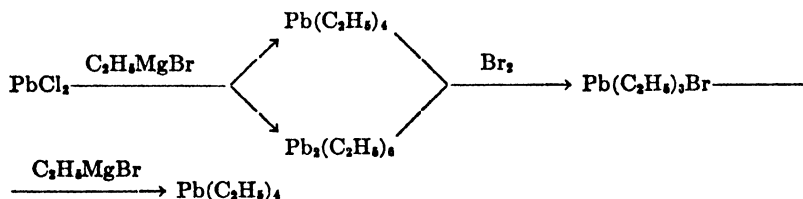
Tetramethyl lead. Lead chloride (1.8 mole) is added slowly to an excess of methyl magnesium chloride (4 moles) in absolute ether under constant shaking. The reaction is completed by heating for two hours on a water bath, and the product is then cooled in ice, decomposed with water, but not acidified. The ether extract is dried over calcium chloride and distilled. The product requires no further purification than a distillation; it boils at constant temperature (110°C.) and melts sharply at −27.5°C.

Tetraethyl lead. The impure tetra ethyl lead obtained by the above method decomposes on distillation. A pure product is obtained with much more ease by the following method: The ether extract is converted into triethyl lead bromide (see procedure, page 49), and the latter is made to react with ethyl magnesium bromide. The product is now completely free from unsaturated lead compounds and does not decompose on distillation.

The last method of preparation is general. Thus, *n.* and *iso*propyl, butyl and amyl lead compounds have been prepared in that way.

Technical lead tetraethyl prepared by the General Motors process described above can now be obtained directly from the Eastman Kodak Company. This commercial product can be used in the preparation of many organic lead derivatives. It can be purified easily and with high yields (90 to 95 per cent) by the following method: The technical product is stirred with an equal volume of sulphuric acid, specific gravity 1.40, the temperature being kept below 30°C. This operation is repeated until the acid layer is colorless. The product is then washed with dilute sodium carbonate and distilled water. After drying over $CaCl_2$ it is fractionated at low pressure in an atmosphere of H_2 or N_2.

The lead sodium reaction, as described under "General Methods of Preparation" can also be used in the laboratory. It has the advantage of being easier to carry out on a larger scale. However, except for the lower members of the series, the yields are low and the product contains varying amounts of Pb_2Alk_6 compound, from which it is difficult to separate a pure $PbAlk_4$. It is nevertheless suitable in the case where it is desired to prepare a trialkyl lead salt without isolating the intermediate alkyl compound in the pure state.

Mixed alkyl compounds. The general method of preparation of organo-metallic compounds reported above gives products in which all the organic radicals are the same. A method has been developed by Grüttner and Krause (12), however, by which it is possible to vary systematically the nature of the organic groups

bound to the metal. They applied it extensively to the preparation of mixed alkyl lead compounds. It is based on the two following typical reactions of tetra-alkyl lead compounds:

$$PbAlk_4 + Br_2 = PbAlk_3Br + AlkBr$$
$$PbAlk_3Br + Alk' MgBr = PbAlk_3Alk' + MgBr_2$$
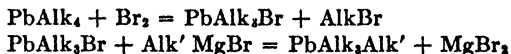
By alternate bromination and reaction with a Grignard reagent, it is possible to prepare compounds in which the four valencies of the lead are occupied by 2, 3 or 4 different alkyl groups.

Physical properties of tetra alkyl compounds

The physical properties of all known alkyl lead compounds are reported in table 1. Unless otherwise specified, the compound has been described in Grüttner and Krause's works (24).

It is possible from an inspection of the data given in Table I to draw some conclusions as to the variation of physical properties through the class of tetra alkyl lead compounds.

The *boiling point* of alkyl lead compounds rises with increasing molecular weight. Of two isomers, the more symmetrical one has the higher boiling point. The influence of symmetry is so great that a compound symmetrical in structure and containing n carbon atoms has a higher boiling point than an asymmetrical compound containing $n + 1$ carbon atoms. For compounds differing only in isomerism of the organic radical, the normal compound boils higher than the iso.

The *specific gravity* decreases with increasing molecular weight. This is the reverse of the case of hydrocarbons, and is simply because the small increase in density due to increase in size of the hydrocarbon radicals is overbalanced by the large decrease consequent to the lowering of the percentage of lead. The effect of distribution of mass is also apparent here, the specific gravity increasing with the symmetry of the molecule.
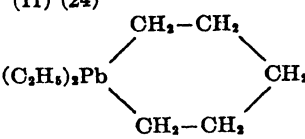
The *index of refraction* decreases with increasing molecular weight. One exception to this rule is that a methyl group gives a lower index than an ethyl group. The index of refraction increasing also with symmetry, the compound with the highest index will be tetraethyl lead. The atomic refraction of lead in

TABLE 1

Physical properties of tetra alkyl lead compounds

LEAD TETRA ALKYLS	B.P. 13 MM.	$d \frac{20°}{4°}$	$n \frac{20}{D}$	REFERENCES, REMARKS
Tetramethyl	110*	1.9952	1.5120	B.P. under 760 mm. M.P. −27.5 (14) (24)
Trimethyl-ethyl	29	1.8824	1.5154	
Trimethyl-*n*. propyl	47	1.7669	1.5095	
Dimethyl-diethyl	51	1.7906	1.5177	
Trimethyl-*n*. butyl	65	1.6777	1.5046	
Trimethyl-*iso*butyl	57	1.6716	1.5026	
Dimethyl-ethyl-*n*. propyl	63	1.6962	1.5118	
Methyl-triethyl	69	1.7130	1.5183	
Trimethyl-*iso*amyl	70	1.5241*	1.4926*	d is $d \frac{21.4}{4}$ n is $n \frac{20.3}{D}$
Dimethyl-ethyl-*iso*butyl	74	1.6240	1.5081	
Dimethyl-di *n*. propyl	77	1.6270	1.5086	
Methyl-diethyl-*n*. propyl	79	1.6422	1.5150	
Tetraethyl	82	1.6528	1.5198	(2) (3) (4) (5) (6) (8) (22) (23) (24)
Dimethyl-ethyl-*iso*amyl	91	1.5595	1.5059	
Methyl-diethyl-*iso*butyl	87	1.5812	1.5117	
Triethyl-*n*. propyl	95	1.5886	1.5168	
Dimethyl-di *iso*butyl	96	1.5048	1.5024	
Dimethyl-n. propyl-*iso*amyl	104	1.5047	1.5028	
Methyl-diethyl-*iso*amyl	103	1.5228	1.5082	
Methyl-ethyl-*n*. propyl-*n*. butyl	103	1.5185	1.5083	
Methyl-tri *n*. propyl	106	1.5241	1.5101	
Triethyl-*n*. butyl	108	1.5292	1.5123	
Triethyl-*iso*butyl	106	1.5313	1.5127	
Diethyl-di *n*. propyl	105	1.5331	1.5149	
Methyl-ethyl-*n*. propyl-*iso*amyl	114	1.4801	1.5068	
Triethyl-*n*. amyl	120	1.4823	1.5097	
Triethyl-*iso*amyl	118	1.4835	1.5099	
Diethyl-*n*. propyl-*n*. butyl	116	1.4817	1.5094	
Diethyl-*n*. propyl-*iso*butyl	110	1.4890	1.5115	
Ethyl-tri *n*. propyl	117	1.4858	1.5120	
Dimethyl-di *iso*amyl	122	1.4302	1.5005	
Diethyl-*n*. propyl-*iso*amyl	126	1.4411	1.5075	
Diethyl-di *iso*butyl	118	1.4440	1.5086	
Tetra *n*. propyl	126	1.4419	1.5094	
Methyl-tri *iso*butyl	122	1.3973	1.5030	
Diethyl-*iso*butyl-*iso*amyl	130	1.3994	1.5050	

TABLE 1—*Continued*

LEAD TETRA ALKYLS	B.P. 13 MM.	$d\,\frac{20°}{4°}$	$20\ n_D$	REFERENCES, REMARKS
Tripropyl-*iso*butyl		1.4056	1.5079	
Diethyl-di *iso*amyl	142	1.3757	1.5041	
Ethyl-propyl-*n.* butyl-*iso*amyl	143	1.3730	1.5035	
Ethyl-tri *iso*butyl		1.3778	1.5064	
Tripropyl-*iso*amyl		1.3819	1.5051	
Ethyl-propyl-di *iso*amyl	145	1.3552	1.5034	
Propyl-tri *iso*butyl		1.3501	1.5054	
Methyl-tri *iso*amyl		1.3153	1.4971	
Tetra *iso*butyl		1.3241	1.5043	
Ethyl-tri *iso*amyl		1.2918	1.4981	
Tri *iso*butyl-*iso*amyl		1.2981	1.5012	
Propyl-tri *iso*amyl		1.2756	1.4979	
*iso*Butyl-tri *iso*amyl		1.2516	1.4960	
Tetra *iso*amyl		1.2337	1.4947	
Trimethyl-*sec.* propyl	80*	1.7403	1.5095	B.P. under 75 mm.
Dimethyl-ethyl-*sec.* propyl	60	1.6962	1.5135	
Dimethyl-ethyl-*sec.* butyl	74	1.6342	1.5128	
Dimethyl-ethyl-*sec.* amyl	88	1.5669	1.5114	
Triethyl-*sec.* propyl	90	1.5812	1.5181	
Triethyl-*sec.* butyl	104	1.5314	1.5186	
Diethyl-di *sec.* propyl	95	1.5220	1.5159	
Diethyl-*n.* propyl-*sec.* propyl	104	1.5355	1.5162	
Dimethyl-*sec.* butyl-*iso*amyl	112	1.4712	1.5066	
Triethyl-*sec.* amyl	118	1.4921	1.5158	
Diethyl-*n.* propyl-*sec.* butyl	114	1.4963	1.5170	
Diethyl-*n.* propyl-*sec.* amyl	121	1.4548	1.5137	
Tetra *sec.* propyl	119	1.4504	1.5223	(11) (24)
Diethyl-cyclopentamethylene	111	1.6866	1.5484	$(C_2H_5)_2Pb$ CH₂—CH₂ / \ CH₂ \ / CH₂—CH₂
Triethyl- ε bromamyl	167	1.6851	1.5374	$(C_2H_5)_3Pb\ C_5H_{10}Br$
1.5 Di trimethylplumbyl *n.* pentane	166	1.9481	1.5556	$(C_2H_5)_3PbC_5H_{10}Pb(C_2H_5)_3$ (25)
Triethyl-allyl	92	1.6085	1.5423	$(C_2H_5)_3PbC_3H_5$ (25) Dec. at B.P. (26)
Trimethyl-benzyl	124*			Dec. at B.P.
Triethyl-benzyl	149*	1.5374*	1.5843*	d is $d\,\frac{23.4}{4}$ n is $n\,\frac{21.4}{D}$ (26)
Tetracyclohexyl				(27) (28)

* See Remarks.

the tetra alkyl compounds varies also with the molecular weight, symmetry, and nature of the Pb-C linkages (primary or secondary), being minimum in $Pb(CH_3)_4$ (AR_D = 17.31) and maximum in $Pb(C_2H_5)_3C_3H_5$(AR_D = 20.12) (25).

The theory has been proposed (23) that the four Pb-C linkages were not of same value in tetra alkyl lead compounds. According to Werner and Jones, the formula best representing lead tetraethyl would be:

$$C_2H_5- + + -C_2H_5$$
$$Pb$$
$$C_2H_5- + - +C_2H_5$$
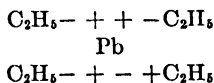
in which three ethyl groups are charged negatively and the fourth positively. Their arguments for the theory are that such a compound easily reverts to compounds of di-valent lead, and that, when decomposed by an acid, it liberates three ethyl groups as hydrocarbons and one as alcohol (or ester):

$$
\begin{array}{ccc}
C_2H_5 - + \quad + - C_2H_5 & C_2H_5 - + & \\
\qquad Pb \qquad \longrightarrow & \qquad Pb \quad + \quad (C_2H_5 + - C_2H_5) \\
C_2H_5 - + \quad - + C_2H_5 & C_2H_5 - + &
\end{array}
$$

$$
\begin{array}{cccc}
C_2H_5 - + \quad + - C_2H_5 & & HOH & \qquad - + \\
\qquad Pb \qquad \quad + & & \qquad = (CH_3 \cdot COO)_2 \quad Pb \\
C_2H_5 - + \quad - + C_2H_5 & & 2HC_2H_3O_2 & \qquad - + \\
& & & \qquad 3(C_2H_5 - + H) \\
& & & + \\
& & & \quad (C_2H_5 + - OH)
\end{array}
$$
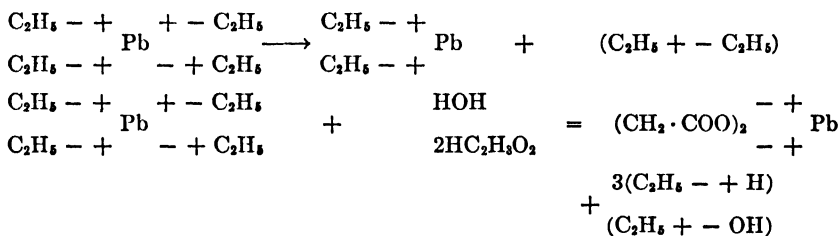
The first reaction never takes place. Quite to the contrary, all evidence points to the fact that the stable valency of lead in its organic compounds is 4: All other compounds revert to that valency whenever possible (see pp. 50–51, and no tetravalent compound goes over to organic compounds of lower valency without the use of strong reducing agents (p. 53).

The only case where tetravalent lead compounds decompose spontaneously into divalent compounds is where two valencies are occupied by inorganic radicals, such as PbR_2Br_2, for instance. Here, the compound is as much inorganic as organic, and tends to go over to the more stable form, $PbBr_2$.

The second reaction is indeed substantiated by experimental evidence:

When lead tetraethyl is decomposed with acetic acid, three ethyl groups are given off as ethane, and the fourth as alcohol (ethyl acetate). However, as will be seen in a later chapter, the replacement of one alkyl group by an acid radical is a very easy reaction:

$$PbR_4 + 2CH_3 \cdot COOH = (CH_3COO)PbR_3 \cdot + R \cdot COO \cdot CH_3$$

and the compound so obtained shows properties very different from PbR_4. This can easily be attributed to the substitution, as is the case, for instance, with methane. The methane molecule is much more resistant to reagents than CH_3OH or CH_3Br, although it has been demonstrated that the four hydrogen atoms occupy positions entirely similar. Thus, the acid first substitutes one of the alkyl group, and in the compound so formed the remaining alkyl groups show a reactivity which is quite different from that of the same groups in a tetra alkyl lead compound.

A decisive argument against the above theory is afforded by the studies of compounds of the type PbR_3R'. Experience has shown that the following chain of reactions takes place:

$$PbR_4 \xrightarrow{Br_2} PbR_3Br \xrightarrow{R'MgBr} PbR_3R' \xrightarrow{Br_2} PbR_2R'Br$$
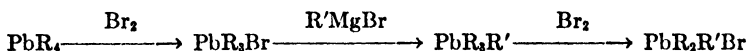
According to Jones and Werner, the bromine will replace the negatively charged alkyl radical in the molecule, and will, in turn, be replaced by the new R' radical, which will thus necessarily become the negative radical. On repeating the bromination on this new compound, the R' radical should thus be displaced. This is in contradiction with experience, which has shown that in all compounds of the type PbR_3R' (with only one exception), the halogen displaces one of the three R groups (12).

We must admit, therefore, that the tetra alkyl lead compounds are symmetrical in structure, the four valencies of the lead atom being identical.

With four valencies of equal value, the tetravalent lead atom could still offer cases of steric isomerism. For instance, if its valencies formed two distinct pairs, there would be a possibility of

existence of cis and trans isomers, as in the case of substituted ethylenes:
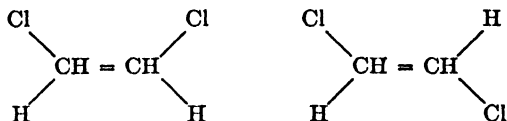
Lead compounds of the type $PbA_2A'_2$, whatever the method is by which they are prepared, always show the same physical properties (24). It is thus highly probable that there exists no steric isomery and that the four valencies are oriented in the lead atom in directions entirely similar to that of the four valencies of carbon in methane.

TETRA ARYL LEAD COMPOUNDS

Although these compounds have not been studied as extensively as the alkyl compounds, enough information is available on the subject to ascertain the characteristics of the class.

Preparation

The aryl lead compounds can be prepared by either the lead sodium or the Grignard reactions:

1. Five hundred grams of ground Pb-Na alloy (8 per cent Na), 500 grams bromobenzol, and 20 cc. of ethyl acetate are heated under reflux for sixty hours. The product is extracted with hot benzene and purified by recrystallization from the same solvent. The yields are low (20 per cent) on account of the predominance of the formation of diphenyl (7).

The influence of the ethyl acetate is not explained, but no reaction takes place between alloy and bromide in the absence of a compound from which the sodium will liberate hydrogen.

2. The Grignard reaction can be conducted in a similar way to that described for the alkyl compounds, care being taken to use an excess of Grignard reagent, in order to avoid the contamination of the product by unsaturated lead compounds (10).

All the tetra aryl lead compounds are while sollids, crystalliz able and of definite melting point. They are insoluble in water,-

sparingly soluble in most organic solvents, and readily soluble in benzene, carbon bisulphide and chloroform. They are very resistant to heat and atmospheric oxygen. Acids, halogens and the halides of heavy metals convert them into di- and tri-aryl lead salts, but with greater difficulty than the alkyl compounds.

Thus, it is possible to prepare diphenyl lead nitrate, by boiling tetra phenyl lead with concentrated nitric acid (7):

$$Pb(C_6H_5)_4 + 2HNO_3 = Pb(C_6H_5)_2(NO_3)_2 + 2C_6H_6$$

while lead tetraethyl, under the same conditions, is converted completely into lead nitrate.

Mixed aryl compounds. They are prepared, like the mixed alkyl compounds, by the action of aryl lead salts on Grignard reagents:

$$Pb(C_6H_5)_2Cl_2 + 2CH_3 \cdot C_6H_4MgBr = Pb(C_6H_5)_2 \cdot (C_6H_4 \cdot CH_3)_2 + Mg\,Br_2 + MgCl_2$$
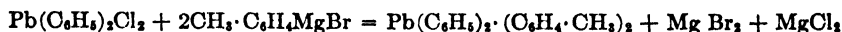
They also are white crystalline solids. They exhibit, however, a lower stability and a greater reactivity and solubility. It seems that once the high degree of symmetry of the $PbAr_4$ compounds is reduced, the molecule is at once made more sensitive to outside influences. Thus, the temperatures of decomposition of the compounds are as follows:

PbAr₄... 270–300°C.
AbAr₂Ar'₂
PbAr₃Ar' .   ... 190–265°C.
PbAlk₄... 100–150°C.

They are more readily attacked by bromine than the $PbAr_4$ compounds, and also react with $AgNO_3$ in aqueous solution to form organo-silver salts, such as $C_6H_5Ag \cdot AgNO_3$, which reaction is not shown at all by the $PbAr_4$ compounds (13).

Mixed alkyl-aryl. These compounds, which are always prepared by Grignard reactions from the corresponding tetra alkyl or aryl compounds, show properties intermediate between those of alkyl and aryl compounds.

The trialkyl aryl compounds are liquids, and can be distilled under reduced pressure. The dialkyl diaryl compounds are

either solids or liquids.   The alkyl triaryl compounds are solids, resembling the tetra-aryl compounds in most of their properties.

In general, it can be said that all the compounds in which the four valencies of the lead atom are satisfied by organic radicals are very similar in properties.   Their physical properties vary

TABLE 2

Physical properties of tetra aryl and aryl alkyl lead compounds

LEAD TETRA ARYL	M.P.	REFERENCES
Tetraphenyl..	225	(7) (10) (27)
Tetra *p.* tolyl.....................................	240	(7)
Tetra *o.* xylyl....................................	255	(13)
Triphenyl-*o.* tolyl....	125	(13)
Triphenyl-*m.* xylyl................................	112	(13)
Triphenyl-*p.* xylyl................................	105	(13)
Triphenyl-*p.* phenetyl.............................	120	(13)
Triphenyl-*α* naphthyl..............................	101	(13)
Diphenyl-di *α* naphthyl............................	197	(13) (22)

ALKYL ARYL LEAD	M.P.	$d\,4^{20}$	REFERENCES
Diethyl-diphenyl..........................		1.6435	(22) (32)
Diethyl-di *α* naphthyl.....................	116		(13)
Diphenyl-dicyclohexyl....................	180		(27)
Triphenyl-ethyl...........................	42		(13)
Triphenyl-cyclohexyl.....................	119		

ALKYL ARYL LEAD	B. P. 13 MM.	$d\,4^{20}$	$n\,D^{20}$	REFERENCES
Trimethyl-phenyl.................	104	1.7376	1.5816	(29)
Trimethyl-*o.* tolyl...............	118	1.7408	1.5793	(29)
Trimethyl-*p.* tolyl...............	119	1.6826	1.5732	(29)
Triethyl-phenyl.................	136	1.5931	1.5757	(29)
Triethyl-*o.* tolyl.................	153	1.5853	1.5740	(29)
Triethyl-*p.* tolyl.................	154	1.5281	1.5686	(29)
Triethyl-*α* naphthyl..............	176 dec.			(29)

with their molecular weight and symmetry.   They all show practically the same chemical properties, varying only in intensity with the size and stability of their organic groups.

The influence of the different substitutions on the structure of the lead atom itself is well illustrated by the variation in atomic

refraction of the lead reported above for the alkyl compounds. A similar determination on triphenyl ethyl lead gave $Ar_{H\alpha}$ = 18.89, which is close to the value obtained from an alkyl compound containing the same number of C atoms:

$$Pb(i \cdot C_5H_{11})_4, Ar_{H\alpha} = 19.05 \cdot (13)$$

The physical properties of all known aryl and mixed arylalkyl compounds are given in table 2.

UNSATURATED LEAD COMPOUNDS

All the compounds studied in the preceding chapter correspond to a tetravalent lead atom. Here and there, however, in their methods of preparation, it has been evident that some compounds are formed corresponding to a different class. The electrolytic reduction of ketones at a lead cathode produces a deep red liquid which, treated with bromine, gives salts corresponding to the formula $PbAlk_2Br_2$ (11). Also, in the action of $PbCl_2$ on Grignard reagents, a red color is first developed which disappears on shaking (29). The same is observed when trialkyl lead salts or alkyl halides dissolved in liquid ammonia are treated with metallic sodium (18). The action of alkyl halides on lead sodium alloys gives a product which is yellow, readily oxidized by air, and separates metallic lead when exposed to light (3). The product obtained in the Grignard reactions have the same yellowish color and instability observed in the lead sodium reactions. From all these observations, it was evident that other organic compounds of lead existed, corresponding to a lower valency of the lead atom. Some of them have finally been isolated and are described below.

Compounds of the type PbR_3 or Pb_2R_6

a. Aryl compounds. These were first prepared by E. Krause and M. Schmitz (33). They observed that, in the aryl series as in the alkyl series, the amount of unsaturated compounds obtained in the Grignard reaction increased with the molecular weight of the organic radical used. But here, instead of being unstable, non-volatile and not crystallizable, like the correspond-

ing alkyl compounds, the aryl compounds were stable solids, which could be recrystallized without decomposition. They proceeded to prepare these compounds in the pure state by the following method:

One-fourth mole of $PbCl_2$ is added in small portions and with constant shaking to 0.75 mole of the Grignard reagent in 400 cc. of dry ether. The solution turns yellow, then brown, and only a small amount of metallic lead separates out. The solution is heated for 2 hours on a water bath. This converts the divalent compound into trivalent compound, as indicated by the color of the solution, which turns back from brown to yellow. The product is decomposed with water and ammonium chloride, and two-thirds of the ether is distilled off. The remainder of the ether contains only a little of the product with most of the impurities. The mass of the product, mixed with the spongy lead under the aqueous layer, is washed with water and alcohol, and then extracted with hot benzene and recrystallized from the same solvent. The yield is over 50 per cent.

The triaryl lead compounds are greenish yellow solids, stable in air and easily crystallizable from benzene. By the action of sunlight they decompose with separation of metallic lead. By the action of bromine, they first form salts of the type $PbAr_3Br$, without the formation of aryl bromides:

$$PbAr_3 + Br = PbAr_3Br$$
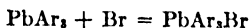
and with an excess of bromine, they give di-aryl lead di-bromides and an aryl bromide:

$$PbAr_3 + Br_2 = PbAr_2Br_2 + ArBr$$
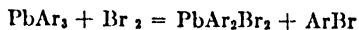
They are soluble in benzene, chloroform, pyridine and alcohol. Their molecular weights in solution show, though to a less marked degree, the same anomalies observed with the hexa aryl derivatives of ethane.

Benzene solutions of concentrations higher than 0.01 mole of Pb_2Ar_6 per 1000 grams contain only the Pb_2Ar_6 compound. At lower concentrations the compounds dissociate into free $PbAr_3$ radicals, the degree of dissociation apparently decreasing with

increasing molecular weight. The figures on the subject are not too reliable, as they are calculated from observed very small freezing-point lowerings, varying between 0.01 and 0.05°C. They are, however, corroborated by the reactivity and stability. One would expect, as is the fact, a compound like $Pb_2(p.C_6H_4 \cdot CH_3)_6$ to be more stable than $Pb_2(C_6H_5)_6$, which dissociates more readily.

b. Alkyl compounds. Only one alkyl compound of this type has been prepared, $Pb_2(C_2H_5)_6$. It was obtained (15) by electrol-

TABLE 3

Physical properties of triaryl lead compounds

TRI ARYL LEAD	DEC. AT °C	CONC MOLES $Pb_2Ar_6/1000$ GRAMS C_6H_6	PER CENT DISSOC. IN $PbAr_3$	REFERENCES
Triphenyl........................	155	0.008 0.001	19 98	(14)
Tri-*o*. tolyl......................	240			(14)
Tri-*p*. tolyl......................	193	0.008 0.001	5 95	(14)
Tri-*p*. xylyl.....................	220	0.008 0.0015	10 100	(13)
Tri-cyclohexyl....................	195			(28)

ysis of a solution of triethyl lead hydroxide in aqueous NaOH:

$$2Pb(C_2H_5)_6{}^+ \ {}^-OH + 2(-) = Pb_2(C_2H_5)_6 + H_2O + 1/2\ O_2$$
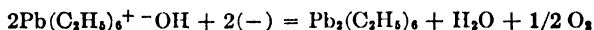
Another method consists in the treatment with metallic sodium of a solution of $Pb(C_2H_5)_3Br$ in liquid ammonia (18).

$$2Pb(C_2H_5)_3Br + 2Na = Pb_2(C_2H_5)_6 + 2NaBr$$
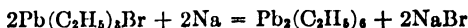
The yields are low in the first reaction and nearly quantitative in the second. Both methods are quite different from those used by Krause in the preparation of aryl compounds. They have apparently not been applied to the preparation of other alkyl or aryl compounds, but there is every reason to believe that they could be used with equal success.

Triethyl lead or di-lead hexaethyl is a greenish yellow liquid of specific gravity 1.94. It can be steam-distilled without much decomposition and boils around 100°C. under 2 mm., but cannot be distilled directly. It is miscible with organic solvents and does not freeze at −80°C. It absorbs oxygen from the air, depositing a brownish yellow solid, and is decomposed by light into $Pb(C_2H_5)_4$ and Pb. It was not obtained as pure as the aryl compounds, as it could not be crystallized or distilled without decomposition.

Molecular weight determinations in benzene solutions show the following percentage dissociation:

MOLES $Pb_2(C_2H_5)_6$ PER 1000 GRAMS BENZENE	DISSOCIATION INTO $Pb(C_2H_5)_3$
	per cent
0.006	30
0.003	100

These figures, although sensible of the same inaccuracy as those reported in table 3 for the aryl compounds, indicate a higher dissociation, corroborated again by the greater instability of the compound.

The action of bromine gives only $Pb(C_2H_5)_3$ Br and $Pb(C_2H_5)_2$ Br_2, and no reaction could be performed which would break a Pb-C linkage in preference to the Pb-Pb bond.

Furthermore, $Pb_2(C_2H_5)_6$ shows to an even greater degree than $Pb_2(C_6H_5)_6$ a tendency to go over to the more stable compound of tetravalent lead:

$$2Pb_2(C_2H_5)_6 = 3Pb(C_2H_5)_4 + Pb$$

Indeed, when exposed to light, $Pb_2(C_2H_5)_6$ goes over slowly to $Pb(C_2H_5)_4$ with deposition of lead and without evolution of gas. At high temperatures, however (140°C.), it explodes violently.

The properties reported here for $Pb_2(C_2H_5)_6$ seem sufficient to prove that the unsaturated lead compounds present in the products of either the lead-sodium or the Grignard reaction belong to the same type: They are all greenish yellow liquids, show the same instability in air, and can be distilled with only partial

decomposition when they are mixed with enough of the tetra-compound to lower their boiling point below the temperature at which they decompose.

That they do not belong to the PbA_2 type will be made evident from the study of these compounds in the following section.

Compounds of the type PbA_2

The existence of these compounds was already suspected by early experimenters. Tafel obtained by electrolytic reduction a dark red oil, highly unstable, absorbing oxygen and CO_2 to give colorless compounds, and adding bromine directly. He wrote the last reaction as follows:

$$Pb(C_3H_7)_2 + Br_2 = Pb(C_3H_7)_2Br_2$$
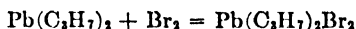
but was unable to isolate his red dialkyl compound in the pure state on account of its instability (11).

Pfeiffer reported that they were formed in the Grignard reaction, but decomposed at once, as was shown by the immediate disappearance of the red coloration (29).

Di-aryl lead compounds.

E. Krause and M. Schmitz were the only ones to prepare divalent organic lead compounds in a pure state (14).

The Grignard reagent solution of 0.2 mole of C_6H_5MgBr is cooled with ice and salt and stirred vigorously. One-tenth mole of $PbCl_2$ is added slowly in a current of nitrogen, care being taken to keep the temperature below 2°C. The product is treated with ice water and extracted with benzene. It is separated from some triphenyl lead by fractional crystallization and finally precipitated with alcohol, all operations being under nitrogen (yield 15 per cent).

Lead diphenyl is a blood-red amorphous solid, very soluble in benzol, less in ether, insoluble in alcohol and water. It is oxidized to colorless compounds by atmospheric oxygen and decomposes at about 100°C. in air. Iodine converts it into lead iodide, with intermediate formation of diphenyl lead iodide:

$$Pb(C_6H_5)_2 + I_2 \rightarrow Pb(C_6H_5)_2I_2 \rightarrow PbI_2 + (C_6H_5)_2$$

At comparatively high concentration (0.008 mole PbAr$_2$), it shows no molecular association.

Di-p. tolyl lead was prepared in the same manner and shows similar properties to those of diphenyl lead.

Di-alkyl lead compounds. As was said above, evidence of the formation of di-alkyl lead compounds is obtained in various reactions but they were never isolated. Attempts were made in the author's laboratory to carry on the following reactions:

$$2C_4H_9MgBr + PbCl_2 = Pb(C_4H_9)_2 + 2MgBr_2 \text{ (in ether)}$$
$$Pb(C_2H_5)_2Cl_2 + 2Na = Pb(C_2H_5)_2 + 2NaCl \text{ (in liquid ammonia)}$$
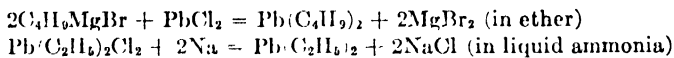
but no dialkyl lead compound could be isolated in either case.

The red coloration observed there as in the Grignard reaction is, however, an indication of their formation, and since Pb$_2$Alk$_6$ compounds are present in the final products of some reactions, the complete mechanism of the reaction must involve either or both of the following series:
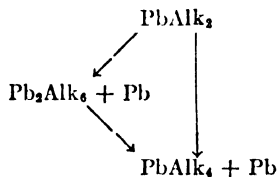
The decomposition of the dialkyl compound is always rapid; that of the dilead hexa alkyl decreases with increasing molecular weight, the tetra alkyl compound being, however, the more stable form in all cases.

ORGANIC LEAD SALTS

Under the heading of organic lead salts are included all the compounds in which one or more of the valencies of the lead are satisfied by inorganic or acid radicals, such as Cl, OH, SO$_4$ and CH$_3$COO.

These compounds differ greatly from the preceding ones, resembling to a certain extent the similar compounds of mercury.

They are, as a rule, white crystalline solids, somewhat soluble in water and in liquid ammonia as well as in organic solvents. Their aqueous solutions are ionized and show the typical reactions of their acidic ions. Their metal ions, PbR_3^+ or PbR_2^{++}, show properties which differ somewhat with the nature of the substituents. In general, the PbR_3^+ ions resemble the alkaline metals; their hydroxides are strong bases, which precipitate the heavy metals from their solutions and displace ammonia from its salts. The PbR_2^{++} ions resemble Zn^{++}; their chloride solutions have a strong acidic reaction, their hydroxides are soluble in both acid and alkali, and their sulfides are precipitated by H_2S as white flocks, soluble in acetic acid and ammonia.

As would be expected, the properties of the organic lead salts in organic solvents are greatly influenced by the nature of the substituents. In the aliphatic series, the solubility increases with increasing molecular weight; in the aromactic series not enough data are available from which to draw definite conclusions. The PbR_3X compounds are soluble in ethyl and methyl alcohol, in benzene and in chloroform. The PbR_2X_2 salts are, at best, only slightly soluble in the above solvents and are more soluble in aniline, dimethyl aniline and pyridine.

The decrease in solubility in organic solvents is usually accompanied by an increase in solubility in water.

Only a few of the organic lead salts show definite melting points as most of them decompose before melting, partly from oxidation and partly by the release of their organic groups. The influence of the acid groups on the stability is also greatly marked, the fluorides and the chlorides showing the greatest stability. No addition compounds are reported for PbR_3X salts. Some addition compounds of PbR_2X_2 salts with pyridine and ammonia have been prepared by Möller and Pfeiffer (29). They were obtained by recrystallizing the salts from pyridine, or by passing dry ammonia gas over them. They are stable, but lose their pyridine or ammonia when exposed to air. They are insoluble in water and in organic solvents.

Salts of the type PbR_3X

Preparation. a. Salts of strong acids. The organic lead salts of strong acids can be prepared by direct action of the acid on the tetra alkyl or aryl lead compound:

$$Pb(C_2H_5)_4 + CCl_3 \cdot COOH = (CCl_3COO)Pb(C_2H_5)_3 + C_2H_5COOCCl_3$$
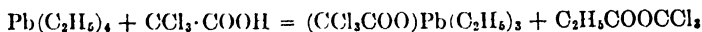
One hundred cubic centimeters (0.5 mole) of tetraethyl lead are put in a beaker with 1 mole of the acid in concentrated aqueous solution, and the two liquids are stirred vigorously. If no reaction has taken place after a few minutes, a slight heating by means of hot water will generally suffice to prime it. The reaction is exothermic, and once it is started, it may be necessary to cool the vessel to avoid complete decomposition. The product, a white solid, is separated from the remaining liquid by pressing and is recrystallized from a suitable solvent.

This procedure gives satisfactory results with CCl_3COOH, HBr, HCl (19).

b. Halogen salts. These can be prepared by direct action at low temperature of the halogens, care being taken to avoid an excess of the latter (20):

$$Pb(CH_3)_4 + Cl_2 = Pb(CH_3)_3Cl + CH_3Cl$$
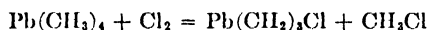
In a 3-liter beaker, CO_2 snow is added to 500 grams of ethyl acetate until it covers the liquid completely. One hundred grams of lead tetramethyl are added, and the mass is kept stirred vigorously. A slow current of chlorine, about 2 bubbles a second, is then passed through the solution by means of a wide tube, until free chlorine becomes visible. This end-point can be detected after a little practice by the change in color. The temperature must be kept below $-60°C$. by continued addition of CO_2 snow. After completion of the reaction the temperature is allowed to rise, the mixture is heated to $50°C$. on a water bath, and the impurities mechanically entrained, together with some dichloride formed by excessive chlorination, are removed by filtration. The solution is concentrated in vacuo, the salt crystallizes out, in well-formed needles which require only to be washed with

ether to give a pure product. The yield is practically quantitative and only traces of $PbCl_2$ are formed.

The above method is general for the preparation of monochlorides and bromides, the bromine being added as a solution in ether.

c. General methods. The salts of the weaker acids are prepared indirectly from the preceding ones, either by double decomposition when one of the products is insoluble:

$$Pb(CH_3)_3Cl + AgNO_3 = Pb(CH_3)_3NO_3 + AgCl$$
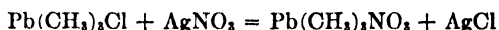
or by saturation of the base by an acid:

$$Pb(CH_3)_3OH + CH_3COOH = (CH_3COO)Pb(CH_3)_3 + H_2O$$

The base itself can be readily obtained by the action of strong alkalis on the halogen salts (3) (15) (30).

Properties. To summarize, it might be said that, in aqueous solution, the PbR_3^+ ions resemble the alkaline metal ions, the solid salts decrease in stability with increasing molecular weight in the aliphatic series, and that the aryl salts are more stable than the corresponding alkyl compounds. With the same R groups, the stability depends on the anion, some of which are listed here in order of decreasing stability: OH-F-Cl-Br-I—

Trialkyl lead salts are not volatile enough to be distilled with steam, but when heated for a few hours in the presence of water, they undergo the following reaction (18):

$$2Pb(C_2H_5)_3Br = Pb(C_2H_5)_4 + Pb(C_2H_5)_2Br_2$$
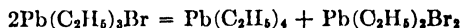
A quantitative yield of the tetra-alkyl compound is formed, while the di-alkyl salt partly loses its organic groups.

This reaction, compared with the similar spontaneous rearrangement of tri-alkyl compounds into tetra-alkyls (18):

$$2Pb_2(C_2H_5)_6 \rightarrow Pb + 3Pb(C_2H_5)_4$$

illustrates the remarkable symmetry of the tetra-alkyl compounds to which all other forms tend to revert.

All available data on PbR_3 salts are given with references in table 4.

TABLE 4
Salts of the type PbR$_3$X

NAME OF LEAD SALT	MELTING POINT	DECOMPOSES	REFERENCE
Trimethyl fluoride..................		305	(30)
Trimethyl chloride................. .	187 subl.		(2) (20)
Trimethyl bromide..................	133 dec.		(2) (20)
Trimethyl iodide.....................			(2)
Triethyl fluoride....................		240	(30)
Triethyl chloride................ ..		170	(2) (3) (4) (5) (10)
			(20) (22)
Triethyl bromide....................	104		(3) (11)
Triethyl iodide................			(2) (3)
Triethyl hydroxide...........		190	(2) (3) (4) (5) (15)
			(30)
Other ethyl salts (nitrate, sulphate, carbonate, phosphate, formate, acetate, butyrate, benzoate).......			(3) (4) (5)
Tri *n.* propyl fluoride.........		235	(30)
Tri *n.* propyl chloride...............	137		(20) (31)
Tri *n.* propyl bromide..............	87		(31)
Tri *n.* propyl hydroxide............		140	(30) (31)
Tri *n.* propyl $\left\{{\text{sulfate} \atop \text{acetate}}\right\}$......... ...			(31)
Tri *iso*propyl chloride.		170–190	(11)
Tri *iso*propyl iodide....			(11)
Tri *n.* butyl chloride..	111		(31)
Tri *n.* butyl $\left\{{\text{hydroxide} \atop \text{bromide}}\right\}$............			(31)
Tri *iso*butyl fluoride.............. .		230	(30)
Tri *iso*butyl chloride.............. ...	122 dec.		(24)
Tri *iso*butyl bromide.................	100 dec.		(24)
Tri *iso*butyl iodide..................			(24)
Tri *iso*butyl hydroxide..............		115	(30)
Tri-*sec.* butyl chloride.............	130 dec.		(19)
Tri *iso*amyl fluoride.................		251	(30)
Tri *iso*amyl bromide.................	132		(24)
Tri *iso*amyl hydroxide..............			(3) (30)
Tri *iso*amyl $\left\{{\text{sulphate} \atop \text{iodide}}\right\}$............			(3)
Tri cyclohexyl fluoride......		198	(30)
Tri cyclohexyl chloride...............	226		(28)
Tri cyclohexyl bromide..............		210	(28)
Tri cyclohexyl iodide................	92–125		(28) (30)
Tri cyclohexyl hydroxide...........			(28) (30)
Diethyl-*e* brom amyl bromide.......			(24)
Triphenyl fluoride..................		318	(30)
Triphenyl chloride..................	206		(26)
Triphenyl bromide..................	166		(26)
Triphenyl iodide....................	139		(14) (26)
Triphenyl oxide....................			(26) (30)
Triphenyl sulfide...................			(26)
Tri *p.* tolyl fluoride.................		280	(30)
Tri *p.* tolyl hydroxide..............			(30)
Tri *p.* tolyl iodide..................	115		(14) (30)
Tri *p.* xylyl chloride................	167	195	(14)
Tri *p.* xylyl bromide...............	177		(13)

Salts of the type PbR_2X_2

Preparation. a. By acids. Some of these salts can be prepared by direct action of the acid:

Thus, on treating lead tetraphenyl with concentrated boiling nitric acid, diphenyl lead nitrate is obtained (7):

$$Pb(C_6H_5)_4 + 2HNO_3 = Pb(C_6H_5)_2(NO_3)_6 + 2C_6H_6$$
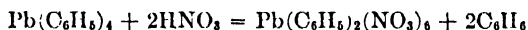
This reaction is successful when working with the very stable $Pb(C_6H_5)_4$ nucleus. With almost any other compound, especially with the alkyl lead compounds, such a drastic treatment would result in a complete destruction of the organic molecule, leaving lead nitrate. The method gave good results with organic acids of medium strength (propionic, valerianic, trichloracetic, oxalic, *p*-nitrobenzoic) but failed to give any results with weaker acids (22).

b. Halogen salts. The dichlorides and dibromides can be prepared by direct reaction on the tetra alkyl (aryl) compounds. The beginning of the procedure is the same as described above for the preparation of the monochloride. As soon as the coloration due to the presence of free chlorine in the solution becomes perceptible, the addition of CO_2 snow is stopped, and more chlorine is passed through the solution with vigorous stirring. The dichloride formed precipitates. When the temperature reaches $-10°C.$, it is kept there by using an ice-salt mixture. The solution is then decanted, and contains no lead compounds. The precipitate is washed by decantation with ethyl acetate, and finally with ether. The yields are quantitative (20).

c. General method. All salts can be prepared by neutralizing the corresponding base with acid. The base itself is readily obtained by decomposing the dihalides with alkalis (20).

Properties. In the aliphatic series, the PbR_2X_2 salts are somewhat less stable than the PbR_3X. They show a tendency to lose their organic constituents to leave an inorganic lead salt, this tendency increasing with increasing molecular weight. In the aromatic series, they are much more stable, as some of them will not even decompose on boiling with concentrated acids.

They are soluble in water, in which they have an acid reaction, only sparingly soluble in alcohol and ether, and more readily in carbon tetrachloride, benzene, chloroform, aniline, dimethylaniline and pyridine.

Some addition compounds have been prepared of diphenyl lead salts with pyridine and ammonia. The pyridine salts, prepared by recrystallizing the salts from that solvent, correspond to the formula $PbR_2X_2, 4Py$. They are insoluble in other solvents and lose their pyridine on standing. The ammonia salts, of the type $PbR_2X_2, 2NH_3$, are obtained by passing NH_3 gas over the salt. They decompose readily when the ammonia gas is replaced by air (31).

The data available on the salts of this type are too scant and too incoördinate to be put in a comprehensive table. For the sake of completeness, a list is given below of all the salts which have been reported, together with the corresponding references:

Salts of the type PbR_2X_2

Dimethyl (20)
Diethyl (11) (20) (31)
Di *n.* propyl (20)
Di *iso*propyl (11)
Di *sec.* butyl (19)
Di *iso*butyl (21)
Di *iso*amyl (24)
Di diethylmethyl (11)
Di cyclohexyl (27) (28)
Methyl ethyl (24)
Ethyl *iso*butyl (24)
Ethyl *iso*amyl (24)
n. propyl *iso*butyl (24)
n. propyl *iso*amyl (24)
*iso*butyl *iso*amyl (24)
Ethyl-ε bromamyl (24)
Diphenyl (7) (9) (10) (14) (22) (31)
di *p.* tolyl (7)
di *p.* xylyl (13)

METHODS OF ANALYSIS

Organic lead compounds are easy to characterize as such, if it is not desired to identify them. Heated in a test tube they decompose to leave a residue of metallic lead, lead oxide or a lead salt, according to the compound investigated. Boiled with a mixture of hydrochloric and nitric acid, they dissolve entirely and give a solution which precipitates $PbSO_4$ by addition of sulphuric acid. When it is desired to detect a compound in dilute solution, the addition of bromine gives a PbR_2Br_2 salt or $PbBr_2$, according to the conditions and the nature of the compound. Either salt will precipitate as a white powder, in which the presence of lead can be ascertained easily. It is not recommended to attempt to concentrate the solutions of alkyl lead compounds before testing as they are volatile enough to distill with the solvent. A better procedure consists in adding an excess of bromine first, and concentrating afterwards if no precipitate is apparent.

With a solution of $Pb(C_2H_5)_4$ in kerosene, it was found that a concentration as low as 0.0005 N is easily detected in that manner.

Quantitative determination of lead

According to Treadwell (32) this is made by treating with an excess sulphuric acid and weighing the lead as sulfate. Polis (7) dissolved the non-volatile aryl lead compounds in concentrated sulfuric acid, and oxidized them to $PbSO_4$ with a permanganate solution. For volatile compounds, a Carius combustion can be made (12).

A better and easier method, applying equally well to all compounds, is as follows (12):

The weighed sample, to which is added 10 times its amount of carbon tetrachloride, is cooled with ice and decomposed by the addition of a large excess of a 10 per cent solution of bromine in CCl_4. The mixture is then heated on a water bath until nearly dry. The precipitate, $PbBr_2$, is boiled for a few minutes with absolute alcohol, cooled and filtered through a Gooch crucible, and washed with a small amount of ice-cold absolute alcohol.

To titrate the amount of tetra alkyl or aryl lead available in a concentrated preparation, the following method is quite accurate and rapid:

Dissolve 1 cc. or 1 gram in 50 cc. of benzol, add aqueous iodine solution in KI in slight excess, shake for a minute or two and then titrate the excess of iodine with standard sodium thiosulfate. The reaction takes place according to the equation:

$$Pb(C_2H_5)_4 + 2I = Pb(C_2H_5)_3I + C_2H_5I$$
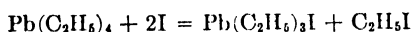
(Private communication from Dr. Graham Edgar.)   This method will, however, not differentiate between PbA_4 and Pb_2A_6 compounds, both using two atoms of iodine:

$$Pb_2A_6 + 2I = 2PbA_3I$$
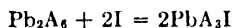
USES

The first investigators of the field of organic lead compounds had apparently no other purpose than to study the properties of new compounds.   The determination of the atomic refraction of the lead, and the preparation of optically active lead compounds were the main incentives to the preparation of scores of compounds.

Working in quite a different field, while they were studying the characteristics of explosions in internal combustion engines, the engineers of the General Motors Research Corporation found that the presence of small amounts of organic lead compounds would prevent detonation or, in other words, remove the objectionable "knock" familiar to all motorists (16).   This resulted in the development of the industrial preparation of tetraethyl lead. The product called "ethyl gas" is a commercial grade of gasoline to which is added 3 cc. of tetraethyl lead per gallon, plus a certain amount of an organic bromide, the rôle of which is to convert the lead into $PbBr_2$ when the fuel is burnt.

According to recent newspaper reports, the use of organic lead compounds as a war gas was investigated during the late wat by the Chemical Warfare Service, but was reported as "not quite poisonous enough."

Two other uses of lead tetraethyl can be mentioned. The first is based on the reaction:

$$4C_2H_5MgBr + 2PbCl_2 = Pb + Pb(C_2H_5)_4 + MgCl_2 + MgBr_2$$
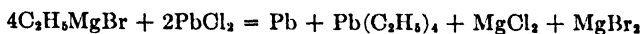
Half of the lead being converted into alkyl compounds while the other half is recovered as metal, it was suggested that this reaction might show a selectivity between lead and its isotope, Radium D. By repeating the reaction a sufficient number of times, it should thus be possible to separate completely the two isotopes. The experimenters successively announced positive and negative results (33), and in the light of the figures available at present, it is still doubtful whether the separation afforded in this way is noticeable.

The second is suggested in a patent (34) which relates to the use of tetraethyl lead in a process of coating iron with metallic lead. It was impossible to find out to what extent the process is being used, but it is interesting in that it is probably the first time that the use of an organo-metallic compound was mentioned in connection with a metallurgical process.

The possibility of uses for organic lead compounds is far from being exhausted. It has been shown that alkyl and aryl lead salts exhibit properties both of metallic salts and of organic compounds. It should be possible by varying the nature of the organic groups to prepare organo-lead ions occupying any desired position in the electromotive series, either coinciding with or intermediate to that of true metals. The use of such radicals may prove to be of value in analytical chemistry. That field has probably not been investigated at all. Metallic cations can be precipitated from their solutions by organic reagents, as is Ni^{++} by dimethyl glyoxime. It is possible that the use of the new organo-metallic ions would effect the separation of anions difficultly separable by the present methods, and perhaps give methods of precipitating some anions of which all known salts are soluble. Furthermore, the compounds so formed could probably be extracted with organic solvents, thus offering another almost entirely new tool in analytical chemistry. Finally, the high atomic weight of lead and the ease with which its compounds

are converted into heavy and insoluble $PbSO_4$ or $PbBr_2$ molecules makes its use of unusual attraction in analytical work.

TOXICITY

Organic lead compounds are more dangerous than the inorganic lead salts on account of their volatility and of the ease with which they penetrate through organic tissues. The odor of alkyl lead compounds is not unpleasant, and therefore does not warn against the danger of breathing them. The salts, especially the more volatile ones such as the tri-alkyl lead halides, are irritating, producing sneezing and tears.

The toxicology of organic lead compounds is almost nonexistent compared with the development of our knowledge of the diseases due to inorganic lead poisoning. Only two papers seem to have been Published on the subject (35). However, some useful information can be derived from the available data. The usual early symptoms of lead intoxication common to organic and inorganic lead poisoning are: Pallor, anemia, stippling of the blood cells, general debility and weakness, constipation, abdominal pain, loss of appetite, and sometimes convulsions. The symptoms observed in cases of tetraethyl lead intoxication differ inasmuch as they show striking mental excitement with appearance of: Sleeplessness, nightmares, hallucinations, headaches, drop of blood pressure and body temperature.

The difference between the two diseases comes from the wide difference between the rate of absorption of the compounds by the organism and of the rate at which the latter is able to react against them.

Inorganic lead compounds are practically not absorbed through the skin, they penetrate mostly through the lungs and the digestive system. Their rate of absorption is thus controlled primarily by their solubility, which is low. At the low concentrations attained, they are at once precipitated in the blood stream as tri-lead phosphate. This is then stored up in the tissues, mostly in the bones and liver, and to a lesser extent in the nerves and the intestines. The characteristic signs of lead intoxication may then not be evident until a relatively large amount of lead

stored up by the organism is suddenly released by a change in the economy of the system (35).

Organic lead compounds, on the other hand, penetrate through the skin and tissues with great rapidity and diffuse probably throughout the organism because of their solubility in fat. The amount of lead which can be present at one time is thus much greater than in the case of inorganic lead. Moreover, the organic compounds are much more resistant to the methods of protection of the organism.

Alkyl or aryl lead salts when submitted to the same reagents as inorganic salts will react much more slowly, if at all, their metallic ion having properties quite different from those of the lead ion. Tetra alkyl or aryl lead compounds will not be reacted upon at all by the precipitating reagents until they are either decomposed by acids or oxidized.

The choice of antidotes for organic lead poisoning should thus be guided by the above characteristics of the compounds. The intravenous injection of sodium thiosulfate has been used in certain cases, on the grounds that this produces lead sulfite, which is extremely insoluble. It seems much more recommendable that in acute cases an antidote be given, which would promote the decomposition of the stable organic compounds. Calcium chloride in intravenous injection probably affords the most promising method of treatment: it is known to increase the acidity of the blood stream, thereby favoring the conversion of the organic lead compounds into inorganic lead salts, which can then readily be precipitated by the phosphates present in the blood (private communication from Dr. J. C. Aub, Harvard School of Public Health.) The calcium chloride has the further advantage of producing a positive calcium balance, thereby preventing the liberation of calcium and lead from the bones, as would be the result of the acidosis in the absence of calcium (36).

Although the organic lead compounds are extremely poisonous, once absorbed, it has been shown by several laboratories that they can be manipulated continuously without danger, providing suitable precautions are taken.

The main points to observe are: To use hoods, preferably with

suction pipes at the level of the table; never to allow the organic lead compounds to come in contact with the skin; to wash with bromine water the utensils which have contained organic lead compounds, and also the walls and shelves in the laboratory, or any corner in which the heavy vapor or dust of the compounds are liable to have settled. Rubber gloves should be used to protect the skin from contact with organic lead compounds. However, since the compounds are readily absorbed by rubber, the gloves should be discarded as soon as they become impregnated.

The aim of this survey is to cover all the information available to date (January 1, 1925) on the chemistry of organic lead compounds. The author hopes that his presentation of the subject will be of some assistance to the reader interested in this particular field of organic chemistry, and that further research may be inspired by it.

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LACTOSE

A REVIEW

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HISTORICAL

Previous to the seventeenth century, milk was considered as composed of casein, butterfat, and serum. Fabritius Bartolettus, philosopher and physician of Mantua, wrote in 1619 (1), "In lacte sunt tres partes,—butyrum, serum, caseus." But in a later book (2), which he probably wrote in 1628, he mentioned a "manna seri" which he obtained by evaporation of milk serum. He spoke of it as "sal seri essentiale, seu nitrum," and described briefly its preparation and purification.

Ettmüller was the next of whom there is record to write of lactose. He described (3) in 1688 the evaporation of the whey and the purification of the crude lactose by recrystallization.

In Venice in 1694 Ludovico Testi (4) advertised lactose as an invention of his own under the name of "saccharum lactis" and advocated it enthusiastically as a remedy for gout and other diseases. The identity of the "saccharum lactis" of Testi with the "manna seri" of Bartolletus was pointed out by Fick (5) a few years later.

In India, lactose had been prepared previous to 1712, since Kaempfer (6) wrote of the "Brahmenes, qui etiam ex omnibus dulcibus, quin ex ipso lacte, saccharum eliciunt."

It was recommended by Stussius (7) in 1713 as an antiscorbutic, diuretic, and febrifuge, and its medicinal use was further discussed by Trostius (8) in 1739. It is interesting to note that most of the affections for which Dyvernois (9) recommended lactose are traceable to improper intestinal elimination and the accompanying autointoxication. He mentioned melancholy,

gout, inveterate itch (possibly urticaria), distemper, and hysterical passion.

In the first half of the eighteenth century, lactose was made on a commercial scale (10) from whey, and, in the last half of the same century, it became a recognized article of commerce (11).

In 1772, Lichtenstein (12) published the first monograph dealing with the chemical and physical properties of lactose.

SOURCES

Lactose occurs in the milk of all mammals with the possible exception of that of the whale. Scheibe (13) claimed that he could account for all the solids of whale's milk as protein, ash, and fat, and that the serum has no reducing action on cupric salts. Takata (14), however, has reported that the milk of Baleaneptera physalus, L., contains 1.8 per cent lactose.

Lactose has been reported from the fruit of Quercus racemosa (15) and from Achras sapota (16), but there is no corroboration for either statement.

It was believed as late as 1888 (17) that milks from different animals contained varying mixtures of different lactoses, but a careful comparison by Deniges (18) in 1893 of samples of lactose from the milks of a number of mammals showed that there is only one natural lactose—or, strictly speaking, one natural equilibrated mixture of stereoisomers—and that the abnormal polarization effects obtained from some milks were due to substances other than lactose. It has been claimed by Pappel and Richmond (19) that the milk of the Egyptian gamoose contains 5.56 per cent of a sugar that gives only d-glucose on hydrolysis. They named this sugar tewfikose.

The lactose content of the milk of various animals is given in table 1. Recent determinations have been selected when available. The single figures represent averages, the pairs of figures extreme values.

BIOSYNTHESIS

The problem of the mechanism of formation of lactose in the animal body has been a troublesome one, and even at the pres-

ent time the theory with the best support is not universally accepted. The problem offers three points for consideration: first, the place of fabrication; second, the agency of fabrication; and, third, the substance or substances from which lactose is formed.

It had been previously generally assumed that lactose is formed in the mammary gland, but the first real evidence was that of Bert (31), who removed the mammary glands of a goat and bred

TABLE 1

Percentage of lactose in milks from various sources

SOURCE	PERCENTAGE	AUTHORITY
Mare............................	4.32-7.56	Hildebrandt (20)
Mare............................	7 9	Folin, Denis, and Minot (21)
Elephant........................	7.27-7.39	Doremus (22)
Woman..........................	5 49-8.35	Denis and Talbot (23)
Woman..........................	7.06	Folin, Denis, and Minot (21)
Ass.............................	6.86	Richmond (24)
Camel..........................	5.78	Dragendorff (25)
Llama..........................	5 60	Doyere (26)
Sheep..........................	5.4	Folin, Denis, and Minot (21)
Buffalo.........................	5.19	Tartler (27)
Goat...........................	5 0	Folin, Denis, and Minot (21)
Cow............................	4.54	Folin, Denis, and Minot (21)
Hippopotamus..................	4.4	Cummings (28)
Indian buffalo..................	4.16	Dubois (29)
Hog............................	4.0	Folin, Denis, and Minot (21)
Cat............................	3 4	Folin, Denis, and Minot (21)
Guinea pig.....................	3.0	Folin, Denis, and Minot (21)
Reindeer.......................	2.21-2.80	Barthel and Bergmann (30)
Dog............................	2 6	Folin, Denis, and Minot (21)
Rabbit.........................	1.8	Folin, Denis, and Minot (21)

the animal. After delivery, glucose appeared in the urine, which Bert took to indicate that the animal could not form lactose in the absence of the mammary gland and hence the gland must be the place of formation. This evidence has been corroborated many times.

Efforts to isolate from the mammary gland an enzyme capable of producing lactose from glucose and galactose have so far failed (32). However, a patent (33) has been issued for conversion of

glucose to lactose by means of a fluid obtained from the mammary gland.

Earlier evidence went to show that there exists in the functioning mammary gland a precursor of lactose analogous to, but not identical with, the glycogen of the liver (34), and one recent investigator (35) supports this idea. While specific evidence against this idea is rather limited, it apparently is not generally accepted.

Whether lactose is formed by a combination of glucose and galactose furnished as such from outside the body, or whether the process consists of a conversion of glucose to galactose, with subsequent or simultaneous combination with more glucose and dehydration, was in doubt up to the early part of the present century. An examination of the foods of herbivorous animals (36) indicated that these animals consumed enough galactose-containing compounds to account for the galactose portion of the lactose which they formed. However, since women and carnivorous animals consume insufficient galactose-yielding substances to account for the lactose which they produce, and since galactose is never found accompanying the glucose in the urine of recently delivered animals whose mammary glands have been previously removed (37), and since efforts to find any substance in the gland that could give galactose by hydrolysis were fruitless (38), the hypothesis of pre-formed galactose as a partial source of lactose has been rejected.

The theory that the mammary gland possesses the power of converting glucose to galactose was advanced three decades ago (39) and has had strong support more recently (40). The considerable amount of work carried out in recent years by Porcher (37) (40) (41) and others (42) brings out the following facts:

1. Removal of the mammary glands before or during pregnancy causes glucose to appear in the urine immediately after delivery; lactose or galactose do not appear.

2. Women who excrete glucose in the urine for a short time before delivery, but who are not true diabetics, excrete lactose in place of the glucose immediately after delivery.

3. Removal of the mammary glands during lactation causes temporary hyperglycemia and glucosuria.

This evidence indicates that lactose is formed in the mammary gland, that its source is exclusively glucose, and that the glucose is supplied from the liver by way of the blood stream. This implies a condensation of pairs of glucose molecules accompanied by a simultaneous internal rearrangement of one member of the glucose pair to a galactose structure.

DISTINGUISHING TESTS

Oxidation of lactose by dilute nitric acid (43) serves to distinguish it from all other sugars except galactose and such as contain a galactose residue. Mucic acid is formed which may be identified by its slight solubility or its titration value (44).

Lactose may be distinguished from glucose and galactose by the use of Barfoed's copper acetate solution (45) or an ammoniacal copper sulfate solution (46), both of which are reduced by the monosaccharides but not by the lactose.

The phenylosazone of lactose cannot be easily distinguished from those of glucose and galactose by its melting point, but it may be identified microscopically (47). Another method (48) of identification is to determine the rotation of 0.2 gram of the osazone in 4 cc. pyridine and 6 cc. alcohol. It should be zero.

Of the various color reactions of the sugars with phenols (49), the yellow-red given by lactose with resorcin distinguishes it from sucrose, which gives a bright red. Phloroglucin gives a red-brown with lactose, a yellow-red with sucrose.

Lactose solution heated with lead acetate (50) becomes yellowish after several minutes. If ammonia solution is added drop by drop, a precipitate forms and redissolves for a time. Then appears a brick-red coloration, next a cloudiness, and finally a cherry-red precipitate with a colorless liquid above it.

A drop of pure diphenylhydrazine heated with a few mg. of lactose and 2 to 3 drops of glacial acetic acid (51) gives a color change from violet through yellow-red and brown-red to dark green. If finally a few cubic-centimeters of diluted alcohol are

added, a characteristic green solution is obtained.　This reaction is said to take place even in the presence of other sugars.

o-Tolylhydrazine gives no hydrazone with lactose itself (52a) but does with its hydrolytic products.　It is a specific reagent for a galactose configuration with a functioning CO group.

Mycological methods have been advocated for distinguishing sugars, particularly those occurring in urine (52b).

<div align="center">DETERMINATION[1]</div>

The uncertainties and difficulties in the determination of lactose in particular and reducing sugars in general are indicated by the large amount of work that has been done in this field. Only in the earliest methods was the lactose itself weighed as such, and then only in impure condition.　Optical properties and reducing power are the bases of practically all modern methods and all such methods are affected by the presence of protein and other sugars.　The lack of stoichiometric relationships in most reducing methods is a further factor that requires careful standardization of manipulations.

Of the substances recommended for removal of protein from milk before lactose determination, there may be mentioned basic lead acetate (53), acetic acid (54), copper acetate (55) (for which is claimed the advantage of removing the dextrin-like substance that often interferes with the polarimetric determination) mercuric nitrate or iodide (56), metaphosphoric acid (57), picric acid (58), asaprol (59), aluminium hydroxide (60), zinc ferrocyanide (61), ammonium sulfate (62), and colloidal iron (63).　The Methods of the Association of Official Agricultural Chemists, 1920, recommends mercury or copper compounds.

Either the polarimetric or cuprimetric methods, or a combination of both, may be used for mixtures of lactose with sucrose, invert sugar, or maltose.　The determinations may be applied before and after partial or complete inversion, or before and after

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[1] Since this article was written, there has appeared an extensive descriptive summary of methods applicable to lactose determination together with an experimental comparison of the principal methods; Bleyer and Steinhauser, Milchwirtschaftliche Forschungen, 1, 131–199, (1924).

fermentation (64).   Sucrose may be inverted by the use of citric acid without affecting lactose (65).   Brewer's yeast may be used to destroy all common sugars but lactose (66).   Bacterium paratyphosi B. will destroy glucose and leave lactose unchanged (67).   Lactobacillus bulgaricus will destroy lactose without affecting sucrose (68).   Saccharomyces anomolus Hansen will completely remove maltose (69).   The proper choice to make among these schemes of separation will be clear from the demands of any particular problem.

Considering now the methods of determination themselves, if we disregard the earlier direct methods such as that of Haidlen (70), we come chronologically to the work of Poggiale (71) (53) and of Fehling (72).   Poggiale developed a polarimetric scheme which did not have much success till Ritthausen in 1878 (55) and Wiley in 1884 (56) applied copper and mercury salts respectively to the task of complete removal of protein from milk. Another difficulty with the polarimetric scheme is due to the error arising from the change in volume caused by the removal of precipitated protein.   This has been solved in several ways. Wiley and Ewell (73) recommend polarizing solutions of two different dilutions and dividing the product of the two readings by their difference.   Others have derived formulae for the conversion of observed to true values (74), and still others have calculated the excess volume of sample to allow in order to neutralize the error (75).   For working directions for this method, those of the Association of Official Agricultural Chemists (76) will be found convenient.

Poggiale also developed the volumetric cuprimetric method (71), employing a single solution containing copper sulfate, potassium tartrate, and potassium hydroxide (77) (78).   The chief variations in this reagent have been in the substitution of ammonium hydroxide (79) and of alkali carbonate (80) for potassium hydroxide, and of citrate (80) for tartrate.   Benedict's method is very popular for reducing sugars and has been successfully applied to the determination of lactose in milk (81).   Folin and Denis (82) have employed a volumetric copper solution containing phosphates for the determination of lactose in small samples of

milk and urine. The iodimetric determination of the excess of unreduced copper is also a somewhat popular method (59) (83).

In the gravimetric field, Fehling (72) developed the idea of keeping the copper sulfate and the alkaline tartrate solutions separate till just before using, but was unable to obtain a constant gravimetric ratio between lactose and copper, though he worked at the problem for twelve years (84). Soxhlet (85) accepted the variation in ratio and found it a gradual variation depending upon a number of factors. He drew up the first of many tables for the conversion of weight of copper to weight of lactose. Much work on gravimetric methods has been done since that time, largely on standardization of conditions and on the forms in which the copper may be weighed. Among these may be mentioned the investigations of Walker (86), Peters (83a), Quisumbing and Thomas (87), and Elsdon (88).

Several colorimetric methods for lactose determination have been devised. Among the colorimetric reagents are sodium hydroxide (89), ammonium hydroxide (90), and picric acid (91).

The Wollny refractometric method (92) is rapid and accurate for fresh normal or watered milk, but is not reliable for milks from sources other than cows (93). An immersion refractometer graduated to read directly in terms of lactose (94) is very convenient for this determination.

The oxidation of lactose to mucic acid by nitric acid may be used as the basis of a method of determination (95), but, since conditions of oxidation and crystallization have a considerable influence on the amount of mucic acid obtained and since only a portion of the mucic acid theoretically possible is ever gotten, it is rather a rough and unreliable method for quantitative work (96).

Oxidation of lactose by potassium permanganate (97) has been employed quantitatively, as has a method based on the oxidation of lactose to lactobionic acid by hypoiodite (98).

HYDROLYSIS AND UTILIZATION

Lactose may be hydrolyzed by the lactase of the intestines of mammals—particularly young mammals—(99), by the lactase

present in almonds (100) and in certain yeasts such as Saccharomyces tyrocola and the Saccharomyces kephir of kephir grains (101), and by dilute acids (102).

For sometime it has been generally agreed that lactose is not directly assimilated by the animal organism, but is hydrolyzed by a lactase to hexoses, which are directly utilized (103). Dastre was awarded the Prix Montyon in 1883 (99) for his researches on this problem. His conclusions were that lactose is utilized through conversion to hexoses, that this conversion occurs in the small intestine, that the agent is the intestinal fluid, that galactose and glucose are the hexoses formed, that these are utilized in the nutritional exchange, and that they may under certain conditions recombine to form lactose. However, Bourquelot and Troisier (103d) fed lactose to a diabetic and recovered in the urine two mols of glucose for each mol of lactose fed and found no galactose. This can be accounted for only by assuming a secondary conversion of galactose to glucose in the digestive tract, since animal lactases in the laboratory convert lactose into equal quantities of glucose and galactose (104). It should be remembered in this connection that in the formation of lactose the reverse change—glucose to galactose—is involved.

Searches for the enzyme hydrolyzing lactose have failed to prove its presence in the pancreatic fluid, the liver, or the stomach (105). It is found plentifully in the small intestine of young mammals, probably being formed at or in the intestinal wall (104a) (106). It diminishes in amount or even disappears with age. It is secreted by birds that have been fed on lactose, though it is ordinarily entirely absent from their digestive tract. Evidence is conflicting as to the point in the digestive tract of birds where the lactase is formed (106a) (107), but its source is probably the crop. It is interesting to note that the intestinal fluid of certain snails is particularly rich in lactase (108).

The fact that beer yeast does not ferment lactose was noted over one hundred years ago (109). That this was due to the inability of the yeast to invert lactose, and that the action of molds was analogous, was not brought out till the time of Berthelot (110) and Fitz (111). Influenced probably by the fact that

alcoholic drinks *were* produced from milk by wild yeasts and by the idea that therefore some yeasts *ought* to ferment lactose, many experimenters tried, without success, to isolate pure yeasts that would ferment lactose. Duclaux in 1887 (112) and Adametz in the following year (113) each reported the isolation of such a yeast. Duclaux's yeast is identical with Saccharomyces tyrocola, and Adametz's Saccharomyces lactis is the same as Saccharomyces kefir (101). A specific lactase is present in both these yeasts, but it is absent from beer yeast. Lactase exists in almonds together with emulsin (114). It occurs also in many seeds, particularly those of the Rosaceae and Cruciferae species (115). The optimum temperature for lactase activity is 37–38°. It is sensitive to phenols, acids, and alkalies.

The acid hydrolysis of lactose will be mentioned again later, but it should be noted here that the weak organic acids do not hydrolyze lactose so readily as they do sucrose (65). For the complete inversion of the lactose in 100 cc. of a 5 per cent solution, Saillard (116) recommends that 10 cc. of 36 per cent hydrochlorid acid be used and the solution be held at 90° for ninety minutes.

BACTERIOLOGICAL

The chief interest of chemists in the bacterial fermentations of lactose lies, not in the species of bacteria that attack this sugar, but rather in the chemical changes brought about by various organisms. Though traces of very many compounds may be found in lactose solutions that have been subjected to bacterial action, the substances formed in any considerable amount are comparatively few.

The lactic acid fermentation (117) is probably the most important and is caused by a number of organisms, particularly those occurring in milk, the most common of which is Streptococcus lactis. This organism is the cause of the normal souring of milk, it is used to hasten the ripening of cream, and contributes to the flavor of many dairy products. Bacterium caucasicus is a lactic organism of some chemical interest (118) because it accompanies the yeast of kefir grains. Lactobacillus acidophilus and

Lactobacillus bulgaricus are lactic acid producers which are used to combat putrefactive organisms in the intestines. These last two will be mentioned later in connection with the use of lactose in the diet. The lactic acid of fermentation may be dextro, levo, or inactive; and it may or may not be accompanied by appreciable amounts of by-products, these differences depending on the type of bacteria concerned (119).

Among the other products of bacterial action on lactose may be mentioned ethyl alcohol (120), viscous gums (121), methane, acetone, acetic acid (122), carbon dioxide, hydrogen (123), butyric acid (121b), (123) (124), acetaldehyde (124a), butyl alcohol (121b) (124b) (125), succinic acid (126), and propionic acid (127). Of these, butyl alcohol, lactic, propionic, butyric, and acetic acids are the only ones formed in any quantity. The commercial utilization of lactose for the manufacture of these substances is impracticable as long as cheaper sugars are available.

The use of lactose by the bacteriologist is largely confined to work with the colon-typhoid-dysentery group of organisms. The bacteria fermenting lactose have been discussed extensively by Levine (128) from the bacteriological standpoint. He defines the colon group as including non-sporing, Gram-negative bacilli which ferment lactose with the production of acid and gas and which are capable of growing aerobically. The typhoid and dysentery types do not ferment lactose, a fact which is made use of in preparing differential media for the isolation of these pathogenic organisms from the members of the colon group which invariably accompany them. The presence of members of the colon group in water supplies is generally assumed to indicate sewage pollution, soil contamination, or proximity of pollution. The members of this group most frequently found in water are B. coli communis and B. lactis aerogenes. B. coli communior and B. acidi lactici are also important members of the group. B. lactis aerogenes and B. acidi lactici are frequently present in milk and contribute to its souring. Spore-forming lactose fermenters are sometimes met with in water samples and of course interfere with the presumptive test for the colon group.

OXIDATION AND HYDROGENATION

A great many different substances may be obtained from lactose by oxidation. The products formed are determined by the choice of oxidizing agent, concentration of oxidizing agent, and the physical conditions of the oxidation.

The auto-oxidation of lactose in the presence of dilute acid (129) results in levulinic acid (γ-ketovaleric), $CH_3 \cdot CO \cdot CH_2 \cdot - CH_2 \cdot COOH$, and formic acid. This reaction may be accounted for by assuming that hydrolysis to the hexoses takes place first, followed by an interchange of oxygen atoms between various groups in the hexose molecules and a splitting out of formic acid and water.

Iodine and lactose heated together in a sealed tube in a steam bath (130) yield formaldehyde, formic acid, and a yellow humic substance which has no reducing power and contains no iodine. Bromine (131) oxidizes the terminal aldehyde group of lactose to carboxyl, thereby forming lactobionic acid, $C_{12}H_{22}O_{12}$. The hydrobromic acid formed simultaneously tends to hydrolyze the lactobionic acid to galactose and gluconic acid, and continued action of bromine gives as final products galactonic and gluconic acids (132). Oxidation of the calcium salt of lactobionic acid (133) by hydrogen peroxide removes the terminal carboxy group and oxidizes the adjacent alcohol group to an aldehyde group, thus producing galactoarabinose, $C_{11}H_{20}O_{10}$.

Lactose is apparently not attacked by ozone (134) or hydrogen peroxide (135) in neutral or acid solution, but is oxidized in alkaline solution. Even air is able to oxidize sugars in alkaline solution (136), hydroxy acids and formic acid being the products. Considerable work has been done by Kiliani and his associates (137) and by Nef (136c) (138) on the various saccharinic acids and their lactone anhydrides, the saccharins. Kiliani's work has been mainly on the products of air oxidation of lactose in the presence of milk of lime. He has identified among these products, α-methylol-α-γ-δ-trihydroxypentoic acid, α-γ-δ-ϵ-tetrahydroxyhexoic acid, and α-ethyl-(ω-ol)α-β-γ-trihydroxybutyric acid. By oxidizing with nitric acid unidentified products of the

reaction, he obtained *d*-tartaric acid, a normal trihydroxyadipic acid, and a tribasic acid, $C_6H_8O_8$.

Solutions of cupric salts react with lactose to give a variety of products; among them, carbon dioxide, formic, lactic, and glycollic acids (139).

The oxidation of lactose by nitric acid to give mucic acid was an early known reaction (140). It has been used as a rough quantitative method of determination of lactose (95), and is a convenient qualitative test for galactose and galactose-containing compounds. The chief products of this oxidation (43) (141) when dilute—25 to 35 per cent—nitric acid is used are the isomeric tetrahydroxyadipic acids, saccharic and mucic, the former derived from the glucose portion of the molecule, the latter from the galactose portion. Tartaric and racemic acids are formed to a slight extent, the tartaric being formed probably by the further oxidation of the saccharic acid, the racemic by the oxidation of the mucic acid. Oxalic and carbonic acids are produced by nitric acid of higher concentration at the expense of the mucic and saccharic acids.

Potassium permanganate in hot acid or alkaline solution oxidizes lactose to carbon dioxide and water (142). However, if the permanganate be of low concentration in the acid solution and be added slowly, considerable quantities of formic acid may be obtained (143). Lactose oxidized with chromic acid is reported to give about 10 per cent of its weight of furfural (144).

Treatment of lactose with sodium amalgam has a number of effects (145). The hydrolysis to hexoses apparently is complete. Hydrogenation takes place to a considerable extent, converting the hexoses into dulcitol and mannitol (sorbitol?). Intramolecular rearrangement, reduction, and further splitting take place to a slight extent, yielding small amounts of sodium lactate, isopropyl alcohol, ethyl alcohol, and hexyl alcohol. The treatment of a water solution of lactose with hydrogen in the presence of nickel (146) gives lactositol, dulcitol, and sorbitol.

CHEMICAL EFFECTS OF HEAT

Lactose hydrate may be heated to 110° without change, but between 110° and 130° it loses all its water of crystallization.

The anhydrous lactose becomes yellow in color at 150 to 165° with no perceptible change in weight (147). At 175° it becomes brown, emitting a characteristic odor and losing about 13 per cent of its original weight. If the heating is not carried above this last temperature, a reaction mass is obtained containing some anhydrous lactose, a substance insoluble in water, and lactocaramel which is water-soluble. For isolation of the caramel, the mass is powdered, warmed with alcohol, and the lactose filtered off. The filtrate is evaporated to a syrup, diluted with water, and again filtered. The filtrate is evaporated to dryness and dried at 100°. Analysis indicates lactocaramel to have the empyrical formula $C_{12}H_{20}O_{10}$. It reduces chromic acid rapidly. It gives no precipitate with barium hydroxide solution, which distinguishes it from sucrose caramel. With ammoniacal lead acetate solution, lactocaramel gives a coffee-colored precipitate insoluble in water or alcohol, but soluble in acid. Apparently the same substance has been obtained recently (148) by dehydration of lactose at 185° for ten to twelve hours under 4 to 6 mm. pressure. The name lactosan has been applied to this compound; constitutionally it is probably 5-galactosyl-glucosan. It polymerizes somewhat during formation and readily in the presence of zinc chloride at 105°.

Pyrocatechin has been identified as one of the products of heating a lactose solution to 280° in a sealed tube (149). If the heating be carried out in a retort with sodium hydroxide solution, a considerable quantity of lactic acid and small amounts of formic acid and pyrocatechin are formed. Fusion of lactose with potassium hydroxide gives small amounts of succinic acid (150).

DERIVATIVES

The phenylhydrazones and phenylosazones of sugars have been of considerable use in distinguishing the members of the sugar group from one another ever since their discovery by Emil Fischer. Lactose phenylhydrazone (151) may be prepared by dissolving one part lactose in one part hot water and, after cooling, adding one-half part phenylhydrazine. After two days standing, this mixture is added to twice its volume of absolute

alcohol. Ether is then added and causes the separation of a yellow syrup. This may be obtained as a colorless solid by redissolving in absolute alcohol and reprecipitating with ether. It is levorotatory. As a class the phenylhydrazones are slightly soluble in water and alcohol. Following is a list giving the properties of a few lactose phenylhydrazones with substituent groups (152):

Lactose amylphenylhydrazone, brown, M.P., 123°, $(\alpha)_D = -8.6°$ in alcohol.
Lactose allylphenylhydrazone, yellow, M.P., 132°, $(\alpha)_D = -14.6°$ in alcohol.
Lactose benzylphenylhydrazone, yellow, M.P., 128°, $(\alpha)_D = -25.7°$ in alcohol.
Lactose β-naphthylhydrazone, brown M.P., 203°, $(\alpha)_D = 0$ in alcohol, $+ 7°$ in glacial acetic acid.

Lactose phenylosazone is made (153) by heating together 1 part lactose, $1\frac{1}{2}$ parts phenylhydrazine hydrochloride, 2 parts sodium acetate, and 30 parts water. On cooling, the osazone separates out as fine yellow needles, melting at 200°, soluble in 80 to 90 parts boiling water, somewhat more soluble in hot alcohol, very soluble in hot glacial acetic acid, insoluble in benzene, ether, or chloroform. Dehydration of the osazone by means of 20 per cent sulfuric acid yields an anhydride which is insoluble in water, ether, or benzene. From hot absolute alcohol it may be crystallized as yellow needles, M.P., 223° to 224° (uncorr.). Phenyllactosazone treated with 5 parts of cold fuming hydrochloric acid (154) decomposes into phenylhydrazine and lactosone $C_{12} H_{20} O_{11}$, in which the secondary alcohol group adjacent to the aldehydic group of lactose has become a carbonyl group. Phenyllactosazone dissolved in a mixture of pyridine and alcohol shows no optical rotation (48). It may be mentioned here that an isolactose has been synthesized from glucose and galactose by the action of kefir lactase (155), the phenylosazone of which melted at 190° to 193°.

Literature records tri-, tetra-, penta-, hexa-, and octonitrates as resulting from the action of nitration mixtures on lactose (156). The octonitrate is probably the best authenticated (157). It melts at 145–146°. $(\alpha)_D^{20°} = + 74.2°$ in 2 per cent solution in methyl alcohol.

Lactose octoacetate, or octoacetyllactose, was first prepared

in 1869 (158) by boiling lactose with acetic anhydride. Herzfeld (159) prepared it later in crystal form by acetylation with acetic anhydride and anhydrous sodium acetate. Proof of the existence of two isomers and the establishment of their properties was only recently accomplished by Hudson and Johnson (160). They acetylated by the second method and obtained octoacetyl-β-lactose which crystallized as microscopic crystals from alcohol and melted to a viscous liquid at 90°. $(\alpha)_D^{20}$ D = $-4.4°$ in 10.6 per cent solution in chloroform, $-23.5°$ in 10.5 per cent solution in benzene, and 0° in acetic acid. The β compound dissolved in glacial acetic acid containing zinc chloride changes slowly to the α form, which has a higher solubility in ether and alcohol. It crystallizes as fine felted needles and melts at 152°. $(\alpha)_D^{20}$ = $+54°$ in 10.6 per cent solution in chloroform, $+28.6°$ in 10.6 per cent solution in benzene, and $+59.9°$ in 10 per cent solution in glacial acetic acid. The equilibrium mixture in glacial acetic acid contains about 86 per cent α and 14 per cent β. Both octoacetates, on treatment with hydrobromic acid, give the same heptaacetylbromlactose. This brom compound gives only the β-octoacetate when treated with silver acetate (161).

Heptaacetylbromlactose may be prepared from lactose and acetyl bromide (162), but the two-stage method is more convenient (163). Octoacetyllactose dissolved in acetic anhydride is mixed with a saturated solution of dry hydrobromic acid in glacial acetic acid. After one and one-half hours the mixture is poured into ice water. The precipitate is dissolved in chloroform, the chloroform solution washed with water and dried, and the substance reprecipitated by addition of petroleum ether. By crystallization from warm alcohol, it is obtained as prisms melting at 143° to 144° (corr.). In chloroform solution, $(\alpha)_D^{22}$ = $+104.9°$; in acetylene tetrachloride, $(\alpha)_D^{22}$ = $+105.16°$. Heptaacetylbromlactose is insoluble in petroleum ether, slightly soluble in water, fairly soluble in chloroform, readily soluble in alcohol, benzene, ether, toluol, acetone, and ethyl acetate. It reduces Fehling solution after short heating. Treatment with silver carbonate and methyl alcohol gives heptaacetylmethyllactoside, M.P., 66° to 67°. $(\alpha)_D^{19}$ = $-5.91°$ in chloroform

solution. Treatment of heptaacetylbromlactose in chloroform solution with silver carbonate and menthol (164) gives hepta-acetyl-β-menthollactoside, M.P., 125° to 130°., readily soluble in the usual solvents with the exception of water, petroleum ether, and ligroin, $(\alpha)_D^{19} = -29.65°$ in acetylene tetrachloride solution. Saponification of this compound gives the β-menthol-lactoside, which crystallizes with 4 molecules of water, M.P., 110°, $(\alpha)_D^{16} = -38.04°$ in acetylene tetrachloride solution. The Fischers claim to obtain a tetradekaacetyltetrasaccharide from heptaacetylbromlactose and silver carbonate, but Hudson and Sayre (165) report a heptaacetyllactose, M.P. 83° (corr.). A thiophenollactoside is obtained by treating heptaacetylbrom-lactose with sodium thiophenylate in ether solution and saponify-ing off the acetyl groups (166). In water solution $(\alpha)_D^{20} = -40.0°$. Its melting point is 221° (corr.). It dissolves readily in cold water and its solution has a bitter taste. It is very slightly soluble in ether, ethyl acetate, or chloroform. Hydroly-sis gives galactose and thiophenol glucoside.

Reduction of heptaacetylbromlactose by zinc and acetic acid (167) involves two secondary alcohol groups and gives hexaacetyl lactal, $C_{24}H_{32}O_{15}$, an unsaturated compound. Saponification of hexaacetyl lactal by barium hydroxide or methyl alcoholic ammonia (168) gives lactal, $C_{12}H_{20}O_9$. It may be obtained as the monohydrate or the anhydrous substance. Lactal is faintly sweet, dissolves readily in water, slightly in hot alcohol or acetone, and not at all in ether or chloroform. It restores the color to fuchsin-sulfurous acid solution and decolorizes bromine water. It is hydrolyzed by lactase to galactose and glucal. Boiling hexaacetyl lactal with water gives a pentaacetyl pseudolactal, which on reacetylation gives hexaacetyl pseudolactal. Saponi-fication of pentaacetyl pseudolactal gives isolactal. Acetyla-tion of isolactal gives hexaacetyl isolactal. The three hexaacetyl compounds differ widely in melting points. Hydrogenation converts hexaacetyl lactal into hexaacetyl hydrolactal. This on saponification becomes hydrolactal, $C_{12}H_{22}O_9$. This compound may also be obtained directly from lactal by hydrogenation. It is slightly sweet, dissolves in twice its weight of water, is

somewhat soluble in hot methyl alcohol, but only very slightly soluble in the other common solvents. It does not show the reactions of an unsaturated compound nor does it reduce Fehling solution. It may be hydrolyzed to galactose and hydroglucal.

Heptaacetylchlorlactose may be prepared by treating lactose with acetic anhydride and dry hydrochloric acid in one operation (169), or by treating octoacetyllactose with dry hydrochloric acid (170). It exists in two modifications, one soluble in ligroin and melting at 57° to 59°, $(\alpha)_D^{20} = +76.2°$, the other insoluble in ligroin and melting at 118° to 120°, $(\alpha)_D^{20} = +73.5°$. The first is probably the α compound and the second the β, since the second gives the β-octoacetyllactose by treatment with silver acetate. The higher melting modification treated with silver carbonate and methyl alcohol (161) gives heptaacetylmethyllactoside, M.P., 65° to 66°, $(\alpha)_D^{19} = +6.35°$ in chloroform. Gentle saponification removes the acetyl groups leaving methyllactoside, M.P., 170° to 171°.

Preparation of the β-acetyliodolactose has been reported by Mills (171). It is claimed that butyryllactose has been prepared by heating lactose with butyric acid (172).

Heptabenzoyllactose may be prepared by treating lactose with benzoyl chloride in the presence of alkali (173). It crystallizes in small rods which melt at 200°. Apparently some penta-, hexa-, and octobenzoyl compounds are also obtained. Hexabenzoyllactose has been reported as melting at 130° to 136° (174).

Aniline and lactose combine with the elimination of water to form a monolactose monoanilide (175). This compound is readily soluble in water, acids, alkalies, dilute alcohol, alcoholic aniline, and alcoholic ammonia. It is slightly soluble in absolute alcohol and insoluble in ether, carbon disulfide, chloroform, and benzene. It reduces alkaline copper solutions and is decomposed in aqueous solution by bromine. $(\alpha)_D = 14.19°$ in water solution. A toluide of lactose has also been prepared.

Lactose is insoluble in ethyl alcoholic ammonia solution, but dissolves in methyl alcoholic ammonia solution, from which after about a fortnight lactose ammonia (176), $C_{12}H_{22}O_{11} \cdot NH_3$, separates as small needle crystals. $(\alpha)_D = -39.5°$. It slowly decomposes into lactose and ammonia in the presence of sulfuric acid.

That a molecular compound of pyridine and lactose exists in solution is indicated by the solubility of lactose in various pyridine-water mixtures (177).

Lactose combines with aminoguanidine salts (178) to form dextrorotatory compounds, — $(C_{12}H_{22}O_{10} \cdot CN_4H_4)_2 \cdot H_2SO_4 \cdot 7H_2O$, $C_{12}H_{22}O_{10} \cdot CN_4H_4 \cdot HNO_3$. The nitrate forms microscopic needles melting with decomposition at about 200°.

Lactose ureide (179), $C_{12}H_{21}O_{10} \cdot NH \cdot CONH_2 \cdot H_2O$, may be prepared from lactose and urea in sulfuric acid solution. It crystallizes in monoclinic needles or plates from 50 per cent alcoholic. $(\alpha)_D = +2.1°$. At 230° it turns brown and at 240° it decomposes. It may be acetylated.

Lactose semicarbazone (180), $C_{12}H_{22}O_{10}:N \cdot NH \cdot CO \cdot NH_2 \cdot 2H_2O$, loses one molecule of water at 115°, the second above 120°, and melts at 185°. Initial $(\alpha)_D = +10.6°$ in water solution, becoming $+11.25°$ after 24 hours. It is soluble in water to the extent of 19.8 per cent at 20.5°.

The octophenylurethane of lactose (181), $C_{12}H_{14}O_{11}(CONHC_6-H_5)_8$, melts at 275–280° and does not reduce Fehling solution.

Ethyl mercaptan reacts with lactose (182), but the lactose mercaptan has not been isolated. Apparently it immediately hydrolyzes to the hexose compound. Hydrogen sulfide does not react with lactose appreciably (183).

By passing carbon dioxide into mixtures of calcium hydroxide and lactose, products containing equimolecular amounts of calcium carbonate and lactose have been obtained (184).

Several patents (185) claim that lactose and formaldehyde form definite compounds, but more recent and extended experiments (186) have indicated that only mixtures of variable composition are obtainable.

By means of the cyanhydrin reaction, lactose may be converted to lactose carboxylic acid (187), $C_{12}H_{22}O_{11} \cdot COOH$. This acid is readily soluble in water, slightly soluble in alcohol, and insoluble in ether. It does not reduce Fehling solution, it forms an insoluble basic lead salt, and on reduction yields a sugar, $C_{13}H_{24}O_{12}$. Hydrolysis converts lactose carboxylic acid into galactose and glucoheptonic acid.

Compounds of lactose with metals have been reported (188), but their properties have not been well defined.

The discussion of the structure of lactose will be limited in this paper to the identity of the hexose sugars involved and their mode of linkage.

The earliest record of the hydrolysis of lactose is by Vogel (102) in 1812. He obtained from lactose and acid a sweet crystalline substance which he supposed was glucose. Erdmann in 1855 (189) showed that lactose on hydrolysis gave a sugar whose specific rotation was not equal to that of glucose. Liebig in 1856 (190) noted the aldehydic reducing action of lactose. Pasteur in the same year (191) found that the sugar which he isolated from the hydrolytic products of lactose gave on oxidation twice as much mucic acid as the same weight of lactose and consequently could not be glucose, but must be a new sugar. Fudakowski in 1866 (192) established the fact that *two* sugars were formed by the hydrolysis of lactose. He found that these sugars differed in crystal form and specific rotation, and that one gave mucic acid on oxidation with nitric acid, but the other did not. He later established differences between the melting points and reducing powers of the two hexoses and applied the names galactose and lacto-glucose (193). The ratio between the elementary components of lactose was first correctly established by Stadeler and Krause in 1854 (194).

In 1888, Emil Fischer (154) converted phenyllactosazone to lactosone by means of fuming hydrochloric acid. Hydrolysis of lactosone gave glucosone and galactose. At about the same time, he and a co-worker (131) hydrolyzed lactobionic acid to gluconic acid and galactose. Fischer reasoned that since lactose forms a monobasic acid on mild oxidation, it must contain only one of the aldehyde groups of its constituent hexoses. It is this aldehyde group that becomes the carboxyl group of lactobionic acid and on hydrolysis, the carboxyl group of gluconic acid. Therefore the aldehyde group of lactose belongs to the glucose portion of the molecule and, on the other hand, the aldehyde group of galactose does not exist as such in lactose, but must

be the point of union of the galactose residue to the glucose residue. Since the aldehyde group and the adjacent secondary alcohol group of lactose must be the groups concerned in lactosazone formation and consequently must become the $-CO \cdot COH$ grouping of Fischer's lactosone, the same conclusion as that above may be drawn from the hydrolysis of lactosone to glucosone and galactose. This conclusion has been further verified by the hydrolysis of various other lactose derivatives to galactose and the corresponding glucose derivatives (108) (133) (167b) (187b), and by work of van der Haar (52), who found that *o*-tolylhydrazine, which is a specific reagent for a galactose configuration with a functioning carbonyl group, gave no hydrazone with lactose. Fischer offered in his paper mentioned above the following linkage for lactose:

$$CH_2OH \cdot (CHOH)_4 - CH \underset{O - CH \cdot (CHOH)_2 \cdot CHOH \cdot COH}{\overset{O - CH_2}{\diagup}}$$

Galactose residue   Glucose residue
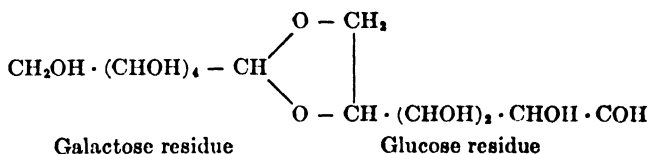
Haworth and Leitch (195) methylated lactose and hydrolyzed the heptamethyl methyllactoside, thus obtaining 2,3,5,6,-tetramethyl galactose as expected (assuming the 1,4-lactone structure for the hexoses) and a trimethyl glucose which they proved, by elimination of the other possibilities, to be 2,3,6,-trimethyl glucose. This proved that it is the 5 carbon atom that is involved in the linkage of glucose to galactose. They give the following linkage for lactose, which is generally accepted as correct:

Galactose residue   Glucose residue
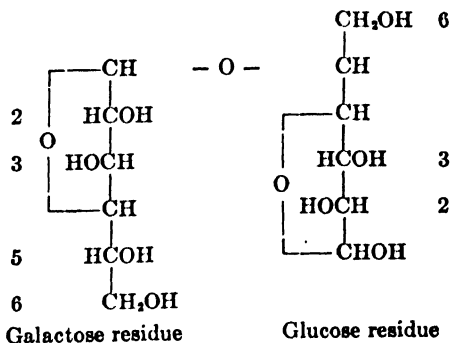
Fischer in his work on enzyme specificity (100) (196) found that an enzyme which would hydrolyze lactose would also hydrolyze a β-methylgalactoside, but not an α-methylgalactoside. On the other hand an enzyme which would hydrolyze an α-galactoside, but not a β-galactoside, would not hydrolyze lactose. Hence he concluded that lactose is a β-galactoside. Perkin (197) gives the evidence of the magnetic rotation of lactose to prove that there is a partial change from an α-glucose-β-galactoside to a β-glucose-β-galactoside when lactose is dissolved in water.

ISOMERISM AND EQUILIBRIA

The earliest statements indicating the existence of more than one form of lactose are those of Erdmann in 1855 (198), who noted the mutarotation of lactose solutions, and those of Dubrunfaut (199), who in the following year recorded that a solution of lactose, saturated at 10° and allowed to evaporate at ordinary temperatures, did not begin to separate out crystals till the concentration had increased from 14.58 per cent to 21.64 per cent. Erdmann (200) and Schmöger (201) worked independently on the mutarotation problem, and established the value of the specific rotation of the hydrate in the vicinity of 84°, that of the anhydride in the vicinity of 39°, and the final value for both in the vicinity of 55°. Schmöger (202) also established the facts that the evaporation of a lactose solution at 100° gives anhydrous lactose, but that the hydrate does not lose water at 100°. Urech (203) measured the rate of change of rotation of lactose to the final value and noted the tremendous accelerative effect of ammonium hydroxide and the milder effect of hydrochloric acid on the rate of change. Tanret (204) apparently was the first to recognize the existence of definitely different modifications of lactose. He listed three forms, — α with $(\alpha)_D = +88°$, β with $(\alpha)_D = +54.6°$, and γ with $(\alpha)_D = +34.5°$. He later concluded that his β form was a mixture of the other two forms (205).

The most extensive investigations on the mutarotation of lactose are those of Hudson (206) and of Gillis (207). They

both considered the closely related subject of solubility relations. The following discussion is based mainly on their results and conclusions.

If a lactose solution is allowed to crystallize at a temperature below 93°, there is obtained the ordinary lactose—that is, the hydrate, $C_{12}H_{22}O_{11} \cdot H_2O$. This is the stable form at ordinary temperatures, since the other forms change below 93° in the presence of water to the hydrate. If the crystallization takes place above 93°, the crystals are anhydrous β-glucose-β-galactoside, or, more briefly, β-lactose (anhyd.). If the more nearly perfect crystals are selected and washed successively with hot glycerine, hot 95 per cent alcohol, and ether, a product of a high degree of purity is obtained. β-lactose (anhyd.) is the stable form at temperatures above 93° as proven by its method of preparation and by the fact that the solid hydrate in the presence of water changes to the β-anhydride above 93°. This form may be preserved indefinitely at ordinary temperatures in the absence of water. If the hydrate is dehydrated at any convenient temperature above 65°, α-lactose (anhyd.) is obtained. This too is not changed in the absence of water, but in the presence of water it changes to the hydrate below 93°, to the β-anhydride above 93°. The α-anhydride heated in contact with a few crystals of the β-anhydride remains unchanges. α-lactose (anhyd.) may be considered metastable at all temperatures in the presence of water. It is α-glucose-β-galactoside, being the analog of α-glucose from the standpoint of molecular rotation and structure.

Since lactose begins to decompose perceptibly at 130°, it is not possible to determine the transition point for α-anhydride ⇌ β-anhydride by ordinary methods. Gillis used the Soch method (208) of determining melting points, which consists of plunging capillary tubes containing the substance into molten baths the temperature of which is close to the expected melting point. He found the melting point of the β-anhydride to be 252.2° and that of the α-anhydride 222.8°. Hence, the transition point is not below the melting point. By the same method, he found the melting point of the hydrate to be 201.6°.

Hudson concluded from his equilibrium studies that the transi-

tion point between the hydrate and the β-anhydride was at 93°. Gillis, using the solubility figures for the β-anhydride and the hydrate and the integrated form of the van't Hoff formula, $nlC = -Q/2T + C$, plotted log C against $10^3/T$. He obtained an intersection of the two curves at a point between $10^3/T =$ 2725 and 2730 corresponding to 93.3° and 93.8°. He therefore assumed 93.5° as the probable transition temperature. Gillis concluded that, since the α-anhydride is always formed on dehydration of the hydrate, the hydrate itself must be of the α form. This is contrary to Hudson's assumption that aldose hydrates have a terminal group-$CH(OH)_2$ which would not permit them to exhibit an α-β asymmetry. This will be mentioned again, but the point of interest here is that, according to Gillis, 93.5° is both a transition and a dehydration point.

The specific rotation of the hydrate is initially about +89°, that of β-lactose initially about +35. After 24 hours, the specific rotation has changed in both cases to the same value, +55.5°. The solution now contains an equilibrated mixture of the two forms. The rates of change of the rotatory powers of both forms correspond to incomplete monomolecular reactions and the constants are the same. Hudson determined the ratio of initial to final rotation at 25° to be 1.55 for the hydrate and 0.64 for the β-anhydride. Gillis obtained 1.61 and 0.63 respectively, working at 0°. Multiplying the specific rotation of lactose in an equilibrated mixture by each of Gillis's factors gives 89.4° as the specific rotation of the hydrate form and 35.0° for the β-anhydride form. Furthermore, by determining the ratio of initial to final rotation for known mixtures of the two forms and plotting composition against this ratio, there is obtained a straight line. At the point where the ratio equals unity—that is, equilibrium,—the solution contains 62.25 per cent of its lactose in the β form and 37.75 per cent in the α form, and the equilibrium constant equals 62.25/37.75 or 1.65 (at 0°).

Gillis has constructed the isotherms for the two forms of lactose below, at, and above 93°, and a space model of the pseudo-ternary system involving lactose and water. These will be found in either of his articles referred to. The fact that no solid

β-hydrate has been isolated is taken to prove that its solubility is greater than that of the β-anhydride.

Hudson's theory of mutarotation as applied to lactose is expressed by the relation:

$$\alpha\text{-anhydride} + H_2O \rightleftarrows \text{hydrate} \rightleftarrows \beta\text{-anhydride} + H_2O$$
$$1 \qquad\qquad 2$$
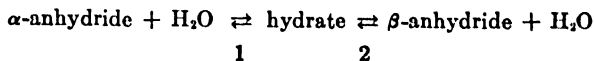
He states that equilibrium 1 is quickly established and equilibrium 2 is slowly established in the case of lactose. He admits that the reverse is the case for maltose and offers no explanation for such a striking difference between otherwise analogous equilibria.

Gillis objects to Hudson's theory on account of the difficulty mentioned above and on account of the assumption of $-CH(OH)_2$ as the terminal group of aldose monohydrates, which denies the lactonic structure of hydrates and the asymmetry of the terminal carbon atom. Hudson himself has shown that the rotational effect of the terminal group of aldoses has a definite additive value which is positive or negative depending upon whether the aldose is of the α or β form. This holds for lactose and would seem to prove that the terminal group of the ordinary hydrate was the mirror image of that of the β form and was identical with that of the α form.

Gillis formulates the lactose equilibria as follows:

$$\alpha\text{-anhydride} + H_2O \rightleftarrows \alpha\text{-hydrate}$$
$$\uparrow \downarrow \qquad\qquad\qquad \uparrow \downarrow$$
$$\beta\text{-anhydride} + H_2O \rightleftarrows \beta\text{-hydrate}$$
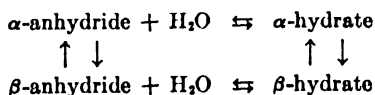
The hydration equilibria become established almost instantaneously and the real cause of mutarotation, according to Gillis, lies in the slower establishment of the equilibria:

$$\alpha\text{-anhydride} \qquad\qquad \alpha\text{-hydrate}$$
$$\downarrow \uparrow \qquad\qquad\qquad \downarrow \uparrow$$
$$\beta\text{-anhydride} \qquad\qquad \beta\text{-hydrate}$$

Gillis points out that his theory does not require the assumption of speeds of different orders for analogous reactions of different sugars.

Leighton and Peter (209) have obtained a definite supersaturation curve for the equilibrium mixture of lactose. This curve lies about 30° below the saturation curve of the equilibrium mixture. In the metastable area between these curves, crystallization can be induced only by the introduction of a sufficient number of suitable nuclei, and it is possible to obtain a slow crystal growth without producing general crystallization. In the labile area below the supersaturation curve, a general crystallization will be produced by any nuclei, but without nuclei crystallization will not necessarily take place. It is possible to carry lactose solutions well into the labile area with the separation of ice alone.

A = supersolubility curve of lactose
B = final solubility curve of lactose
C = initial solubility curve of α-lactose
DD = points on initial solubility curve of β-lactose
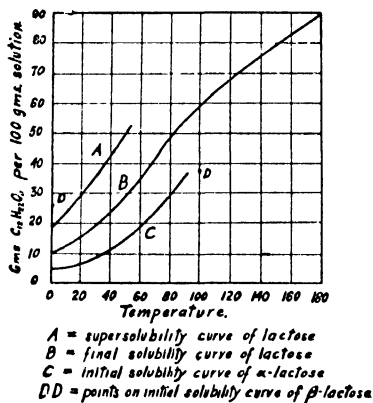
FIG. 1. SOLUBILITY OF LACTOSE

Herewith are included solubility curves constructed on the values of Hudson (206), Saillard (116), and Gillis (210), and the supersaturation curve just discussed.

GENERAL PHYSICAL DATA

Lactose hydrate is insoluble in 95 per cent ethyl alcohol, methyl alcohol, and ether, soluble to about 2 per cent in pyridine (211), soluble somewhat in warm acetic acid, either concentrated or dilute, from which it crystallizes unchanged on cooling (212). It dissolves in about 6 parts of cold and 2.5 parts of hot water and crystallizes therefrom in rhombic prisms. The taste of lactose is less sweet than that of sucrose and, on account of the low solu-

bility and the hardness of its crystals, it produces in the mouth a sensation like that produced by sand.

The ratio of the axes of the crystals is given by Schabus (213) as a:b:c = 1:0.6215:0.2193, and by Traube (214) as a:b:c = 1:0.3677:0.2143. Traube also gives 109° 47′ as the value for β. The cubical expansion coefficient of lactose is 0.00911 per degree between 0° and 100° (215).

The values for the heat of combustion of lactose show so much

TABLE 2

Heat of combustion of lactose

HYDRATE		β-ANHYDRIDE		AUTHORITY
cal./gram	*Cal./mol.*	*cal./gram*	*Cal./mol.*	
3945	1420	4162	1423	Van Rechenberg (216)
3663		3877	1326	Stohmann (217)
3777				Berthelot and Vielle (218)
3724		3920		Gibson (219)
3951	1351	3737	1345	Stohmann and Langbein (220)
3737				Emery and Benedict (221)
3953				Karrer (222)

TABLE 3

Heat of solution and transition of lactose.   20°C.

	HYDRATE	α-ANHY-DRIDE	β-ANHY-DRIDE
	cal./gram	*cal./gram*	*cal./gram*
Initial heat of solution..........................	−12 0	+7.3	−2.3
Final heat of solution............................	−11.4	−7.9	−2.7
Temperature coefficient of heat of solution........	0.1		
Heat of transition to β-anhydride................	+1.0	+1.0	
Heat of transition to equilibrium mixture.........		+1.03	

variation that the principal ones are given in table 2. The heat of formation of the hydrate is given as 535.6 Cal./mol., of the β-anhydride 610.8 Cal./mol. (220). The specific heat of the hydrate is 0.299, of the β-anhydride 0.2895; the molecular heat of the solid hydrate is 107.6 cal., of the solid β-anhydride 99 cal.; the apparent molecular heat of either form when dissolved in water is 147 cal. (223). Table 3 (224) gives values for heats of solution and transition of the various forms of lactose.

The earliest determination of the specific gravity of lactose was probably that of Lichtenstein (12), who found it to be 1.543. This value is surprisingly close to that of Fleischmann and Weigner (225), who calculated from the equation given below the specific gravity of "liquid" lactose and found it to be 1.5453. These workers extended the tables of Schmöger (201b) for observed specific gravity of lactose solutions up to concentrations of 69 per cent and derived the equation,—S_x = 0.9982 + 3.7585 $(10^{-3}X)$ + 1.1284 $(10^{-5}\ X^2)$ + 5.8405 $(10^{-8}X^3)$, in which S_x is the specific gravity of a solution containing X per cent lactose. S_{100} = 1.5453. From a comparison of specific gravity
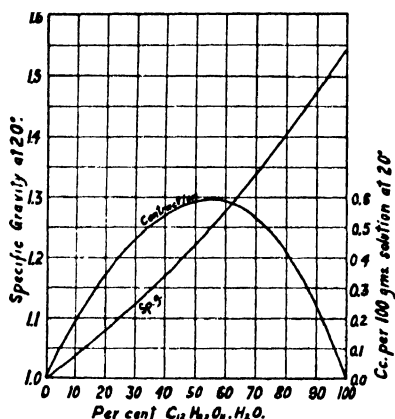
FIG. 2. SPECIFIC GRAVITY AND CONTRACTION OF LACTOSE SOLUTIONS

values calculated on the assumption of no contraction and the actual values obtained, they calculated the contractions of lactose solutions of various concentrations and derived the equation: K = 0.34382X − 0.0031819X^2 − 8.692, in which K is the contraction in cc. for 100 gms. of solution at 20° containing X per cent lactose. The maximum is 0.593 cc. per 100 grams solution and occurs at a concentration of 54.03 per cent lactose. A solution of this concentration contains 18 mols H_2O for each mol of $C_{12}H_{22}O_{11}$. The molar volume of hydrated lactose is 235.2. It has been pointed out (226) that this value is equal to that of the volume of 12 mols of water as ice.

The accompanying plots of specific gravity and contraction are constructed on the values of Schmöger (201b) and Fleischmann and Weigner (225).

MANUFACTURE

The manufacture of lactose is usually carried out in connection with cheese manufacture, since the whey which is the source of lactose is a by-product of the cheese industry. Furthermore, the whey is perishable in so far as its lactose content is concerned and is too bulky to ship profitably. Any scheme for lactose utilization must take these facts into account.

Up to about 1880, lactose was produced only in Canton Luzern, Switzerland. Shortly after this, factories were established in Germany and the United States. In 1893, one factory in New York reported the production of over 250,000 pounds. In 1914 there were produced in the United States 3,500,000 pounds, distributed among sixteen factories. The production for 1922 had dropped to 2,190,000 pounds. Domestic production is somewhat irregular, due to trade conditions and the limited demand.

The original Swiss method (227) was to prepare a crude "sugar sand" at the small cheese factories high in the Alps. This was brought to a central point for refining. The whey was evaporated over direct wood fires in more or less open huts. Evaporation was continued till the whey was of the consistency of syrup or honey and would fall in sheets, "zu blätteln," from a spoon. It was then run into shallow pans and allowed to crystallize for forty-eight hours. The more rapid the cooling and the lower the final temperature, the better the quality and the higher the yield of the sugar sand. Care was taken that the crystals should be neither too fine nor too coarse; in the first case, too much sugar would be lost during washing; in the second case, the impurities could not be effectively removed. The oily mother liquor was poured off and concentrated further to obtain a second crop of crystals. The crystals, after removal of the mother liquor, were stirred with water two or three times, the first two washings being used for hog feed, the last being added to another batch of whey. The sugar was then allowed to drain for a time and sacked for shipment to the refinery.

This process gave about 2.0 to 2.5 per cent of the weight of the whey as crude sugar, or 1.2 to 1.5 per cent as refined lactose. If the lactic acid present was neutralized with lime before evaporation to prevent inversion, yields of lactose as high as 4 per cent of the whey were often obtained. Another method of improving the yield was to dialyze out the salts from the first mother liquor and then add the liquor to a new batch of whey. Concentration by freezing was sometimes used to save fuel.

In the refinery the sugar sand was dissolved in water at 75° and the solution heated to boiling. About one per cent of alum was added and the liquid gently boiled. The scum of impurities was removed and the solution run through a charcoal filter. It was then evaporated "zu blätteln," run into a copper-lined wooden vat, and allowed to crystallize on a raised network of sticks. After four or five days the crust of crystals on the surface would begin to sink and the crystallization was considered complete. The better grade of crystals were shipped, the poorer were purified again.

The more modern methods for lactose manufacture use to a considerable extent the equipment of the cane and beet sugar industry. Lactose solutions are particularly susceptible to the action of heat and the use of a vacuum pan for evaporation is of great assistance in obtaining a white product.

The modern process may be outlined as follows (228): Any butterfat present is removed by a separator. Albumen may be removed by heating nearly to boiling after addition of acetic acid, or it may be left in the whey till later. The whey is then evaporated under vacuum at 60° to 70° until it contains about 60 per cent solids. It is then run into iron crystallizers holding about 174 gallons. These crystallizers have water jackets in which cold water is circulated. For ten hours, or often longer, the mass is frequently stirred to equalize the temperature. After about 24 hours it has become a thick, coarse-grained, yellow mush. This is centrifuged and yields about 3.8 per cent of the weight of the original whey as wet raw sugar containing about 88 per cent lactose.

The mother liquor is then boiled by direct steam to coagu-

late the albumen, which is removed. The clear liquid is then concentrated in vacuo as before and more lactose crystallized and centrifuged out. About 0.5 per cent additional yield of sugar is obtained, making a total yield of about 4.3 per cent of the weight of the whey. The second mother liquor is mostly run to waste or worked up for fertilizer, though efforts have been made to utilize it for fattening hogs, for the preparation of lactic acid, and as a basis of a food product similar to meat extract.

For refining, the raw sugar is dissolved in water at 50° till the solution registers 13° to 15° Bé., or contains 24 to 27 per cent of the sugar. Powdered bone black and acetic acid are added. It is then heated nearly to the boiling point and a small quantity of magnesium sulfate added. The liquid is then boiled till it is decolorized. Considerable foaming occurs and a flocculent precipitate of protein and phosphates separates out. This precipitate is filterpressed, washed, and treated with sulfuric acid to produce a fertilizer high in nitrogen and soluble phosphoric acid. The filtrate is evaporated in vacuo until it registers 35° Bé., equivalent to about 65 per cent solids. It is then crystallized and centrifuged.

Two more crops of crystals are obtained by further evaporation. The refining process is repeated till the desired quality of lactose is obtained. The purified product is dried in a rotating air dryer till the particles will not cohere when pressed between the hands. It is ground in an edge-runner mill and sifted to such a fineness that particles cannot be felt between the fingers. The weight of the finished lactose should average 2.5 per cent of the weight of the whey. The remainder of the lactose of the whey is partly lost by fermentation and by inversion and partly held in solution in the various discarded mother liquors. The other constituents of the whey have a considerable inhibitory action on the crystallization of the lactose.

Several other methods of obtaining lactose from whey have been suggested, among which may be mentioned the evaporation of whey to dryness and the extraction of the lactose with water (229); the evaporation of whey on kieselguhr or other absorbent material with subsequent leaching of the lactose (230); and

evaporation with moderate heat, extraction of the albumen with a limited amount of water, and finally extraction of the lactose (231). Due to interest in soluble milk albumen, it is possible that existing factory methods for obtaining lactose from whey will be largely modified to include production of albumen.

QUALITY, SPECIFICATIONS, AND USES

Examination of seventeen samples of domestic lactose by England (232) indicated that the following specifications for lactose are reasonable:

Sugar of milk of acceptable quality must be a fine, white, dry, odorless powder of not less than 99.7 per cent strength by the polariscope, containing not more than 0.020 per cent nitrogen, not more than 0.020 per cent fat, and yielding not more than 0.050 per cent ash. It must comply with the U. S. P. heavy-metals test and be neutral to litmus paper. A ten per cent solution must be odorless, colorless, and free from mechanical impurities.

For bacteriological use, lactose must satisfy certain additional tests (233). It should prove to be free from alcohol by the iodoform test and contain not more than 0.15 per cent moisture. A 10 per cent solution should show not more than a negligible turbidity when tested for sulfates with barium chloride or for chlorides with silver nitrate. A 10 per cent solution sterilized for thirty minutes at 120° should show a pH value not greater than 4.0 and should remain acid on cooling. d-glucose should be absent as proven by failure to produce acid with Bacterium typhosi B. or to produce gas with yeast. Incubation of a sterilized solution should show no growth.

The literature on the relative value of lactose and other sugars in nutrition is in such an unsatisfactory state that few definite well-founded statements can be made. Instinctively, we are led to believe that because lactose is the sole sugar occurring in milk it must possess some unique characteristic which makes it peculiarly valuable in nutrition. Lactose does differ in some respects from each of the other sugars, but, from the standpoint of nutrition, it is difficult to decide what property or properties

give it any advantage over other sugars. The fact that it is fermented only by certain types of organisms is as good a guess as any. On the other hand, it has been seriously argued (234) that sucrose should be substituted for lactose in infant feeding for such reasons as the non-identity of the lactose of bovine and of human milk, the impurities in commercial lactose, the great danger from the large quantities of lactic acid formed from lactose, and the purgative effect of lactose in large daily doses (235). Another writer (236) advocates for addition to artificial diets for children a mixture of 40 per cent lactose, 40 per cent sucrose, and 20 per cent maltose. The personal tolerances and other idiosyncrasies of the subjects of experimentation are probably as important factors in the reaching of such conclusions as the scientific knowledge and personal prejudices of the experimenter. The fact remains that large quantities of lactose are consumed in milk and milk products, that lactose is used in considerable amounts in proprietary infant foods, and that it is prescribed quite generally by physicians for modifying cow's milk for infant feeding.

If lactose or milk be fed to animals or human subjects in such quantities that the lactose is not all split in the small intestine, the excess may be utilized by lactose-fermenting bacteria, of which B. coli communis and Lactobacillus acidophilus are the chief intestinal representatives. The effect of lactose on the intestinal flora has been extensively investigated by Rettger and his associates (237). They find that feeding lactose or dextrin will change the flora of the large intestine from a putrefactive type to a fermentative type and that the fermentative organisms are almost entirely Lactobacillus acidophilus. The change is considerably accelerated if cultures of this organism be fed together with the sugar. None other of the common sugars produces this result. This is explained by observations that lactose and dextrin alone of the saccharides used succeed in reaching the ileocaecal valve before being absorbed; hence these are the only saccharides capable of stimulating the multiplication of this organism. The frequently advanced explanation of the disappearance of the putrefactive organisms when lactose is

fed—namely, that Lactobacillus acidophilus produces a high acid concentration in the intestine that the putrefactive organisms cannot survive but that it can survive itself—is disputed by Rettger, who failed to find any appreciable change in the H-ion concentration of the intestinal contents after implantation of Lactobacillus acidophilus. Very beneficial results are being obtained by the use of cultures of Lactobacillus acidophilus in milk for the treatment of autointoxication. It should be pointed out that, while Lactobacillus acidophilus is a normal inhabitant of the intestine and can be easily maintained there, Lactobacillus bulgaricus, in spite of the contrary assumption, cannot be implanted and maintained in the intestine. The successful therapeutic use of cultures of this organism has been shown to be due to the stimulation of Lactobacillus acidophilus by the increased quantities of lactose fed with the bulgaricus cultures.

The therapeutic value of lactose is not confined to the action just discussed but includes its pronounced laxative and diuretic effects (238). It is often somethat difficult to separate sharply the laxative effect from the effect of the change of intestinal flora. Both the laxative and the diuretic effects are due probably to the dehydrating action of lactose.

In addition to the uses already mentioned, lactose is used by confectioners in certain types of candies; by manufacturing pharmacists as a sweetener, diluent, and vehicle in the preparation of medicines in tablet form; and by the manufacturers of certain liqueurs on account of the frosty appearance produced by crystallization of lactose on the inside of the bottles. The total consumption of lactose in this country is far less than the amount that could be produced from our dairy wastes; consequently, it is demand rather than potential supply that determines the extent of manufacture of this sugar.

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RECENT STUDIES ON REVERSIBLE OXIDATION-REDUCTION IN ORGANIC SYSTEMS

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INTRODUCTION

Previous to 1920 there had been several attempts to extend potentiometric methods to the study of organic, oxidation-reduction systems. Abegg, Auerbach, and Luther in their practically complete summary of potential measurements mention a few such studies which had found their way into the literature up to 1915. But significant as they are they are not comparable in quality with the more exact of the measurements on inorganic systems and they form but a diminutive body of data compared with the inorganic. Yet it must have been obvious from the first that if reversible cells could be constructed with organic solutes their unlimited variety could be made the means of attacking numerous fundamental problems. Why then had there been so little success?

Such a question can be answered adequately only by one who is familiar with those unpublished discussions which I believe must have enlivened the laboratories of a generation or so ago. I can only suggest some possible reasons for the scarcity of published data.

For one, the attractiveness of preparing organic compounds by electrolytic processes inevitably diverted attention from equilibrium states to a variety of dynamical problems of seemingly more direct practical importance. Thus, even the study by Haber and Russ (1904), which is often quoted now that the equilibrium data for the quinone-hydroquinone system have become of great interest, was more or less incidental to a study of a problem in electrolysis.

Second, the failure to obtain equilibrium potentials with certain organic systems burdened the whole subject with an incubus which might equally well have arisen from inapt choice of inorganic material. The signal success of potentiometric methods applied to metal-metal ion systems has not been paralleled by an equal success of such methods applied to many common inorganic oxidation-reduction systems.

Third, requirements for the stability of most inorganic systems and for the action of many reagents used for the oxidation or reduction of organic compounds led in general to familiarity with strongly acid and strongly alkaline solutions. It required the necessities of the living cell to force upon the biochemist familiarity with the intermediate range of hydrion concentrations. Then there arose a general appreciation of those controlled conditions which we shall see are essential to the potentiometric study of many organic systems.

Fourth, a mistaken concept was responsible for failures with certain organic systems which we now know are amenable to potentiometric measurement. In some of the older papers there will be found attempts to measure the potential-difference between an electrode and a solution containing what was presumed to be the oxidant alone or the reductant alone. We shall see that in such a case the potential-difference becomes indefinite and that any approach to constancy indicates a finite ratio between oxidant *and* reductant. The heroic efforts to measure the potential of a pure solution of a reductant are evidence of the tenacity of a preconception which demands explanation. Clark (1922, pages 255–256) suggests it was "due to the emphasis which had been placed upon the final, working form of the equation for the difference of potential between a metal and a solution of its ions." In obtaining the final form of this equation certain assumptions have been made and the potential difference is made to appear as if it were dependent only upon the concentration of *one species*, namely, the metal ions.

Last, and perhaps most important of all the reasons for scarcity of data, is the difficulty which will be briefly discussed at the conclusion of this article.

I shall not attempt to review the older literature. Much of it is valuable but requires detailed discussion to develop the points of interest. That part of the recent work to which I shall for the most part confine this review admits concise formulation.

In 1920 three groups of investigators quite independently of one another published upon the problem which had long been neglected.

The dissertation of Granger, a student of Nelson (cf. Granger and Nelson, 1921) dealt with equilibrium potentials of quinone and hydroquinone in equilibrium with quinhydrone, demonstrating a good stability and reproducibility of potentials in acid solutions and data in fair agreement with the van't Hoff isotherm.

At the same time Clark (1920) brought to the problem the modern methods of hydrion control which greatly simplify the experimental segregation of variables. The oxidants and reductants were kept at concentrations relatively very small compared with those of a buffer system and thus the ratio of oxidant to reductant could be varied with almost negligible variations of acid-base dissociation. Measurements were then repeated at various pH values to reveal the effects of acidic or basic dissociations of reductant and oxidant. Thus there were obtained preliminary data on methylene blue-methylene white mixtures and on the mixtures of an indigo sulphonate with its reduction product.

The effect of hydrion concentration upon the electrode potential-difference was Biilmann's (1920) chief theme in another paper on the quinone-hydroquinone system. Since quinhydrone in acid solutions furnishes a definite ratio between oxidant and reductant, and since the reductant is a diacidic acid, it follows (as will be shown in detail later) that an electrode in contact with a quinhydrone solution exhibits a potential-difference which in acid, buffer solutions is a linear function of pH. Therefore, as Biilmann demonstrated, the "quinhydrone electrode" can be used for the determination of pH values in acid, buffered solutions.

Since the publication of these three independent papers in 1920 there have been many interesting developments. LaMer

and Baker, Conant and his coworkers, Biilmann and his co-
workers, the investigators at this laboratory and several others
whose important contributions I shall discuss have been develop-
ing the subject rapidly.

I shall illustrate experimental methods by means of only one
case which will suffice to show the more important principles.
Then I shall outline one of several procedures for the development
of equations. With a convenient method of formulating the
somewhat complex relations which will be encountered we can
proceed rapidly. We shall not only gain a better understanding
of how it is that accurate data on organic systems are now being
obtained but we shall also see that the potentiometric methods
are furnishing precise data on free energy relations, opening new
methods of analysis, broadening the methods of determining
hydrion concentrations, aiding in the solution of problems in
structural chemistry, furnishing valuable data on the effects of
substitution, and suggesting new approaches to fundamental
problems of biological oxidation-reduction.

EXPERIMENTAL METHOD

So many experimental procedures are available that I shall
attempt only to illustrate main principles by a specific case.

Let it be proposed to determine the oxidation-reduction char-
acteristics of indigo carmine.

In the next section it will be made clear by means of equations
that the potential-difference between an electrode and a solution
containing indigo carmine and its reductant, leuco indigo carmine,
is determined both by the ratio of the oxidant to reductant and
by the hydrion concentration. Therefore it simplifies the prob-
lem if in one case the hydrion concentration is kept constant while
the ratio of oxidant to reductant is varied and in the other case
the ratio is kept constant while the hydrion concentration is
varied.

The hydrion concentration can be kept practically constant by
means of buffers if the dye which is added be kept at relatively
very low concentration.

A buffer solution is drawn into the bulb S of figure 1 making

liquid junction there with the saturated KCl-solution of the calomel half-cell C. The vessel A is rinsed with fresh buffer solution and put into place with 50 cc. of buffer solution. This is then deaerated with a stream of oxygen-free nitrogen in order to prevent air-oxidation of the leuco indigo carmine which will presently be added.
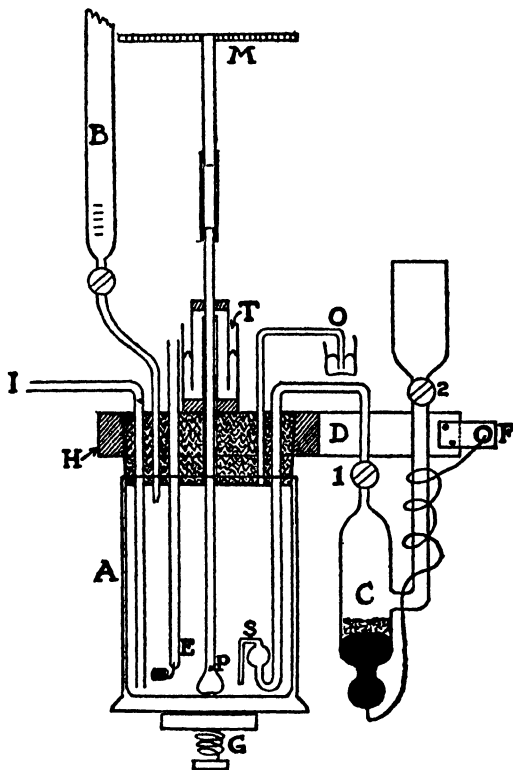
FIG. 1. ELECTRODE VESSEL

There will now be determined the effect on the gold electrode E of variations in the ratio of indigo carmine to leuco indigo carmine. Several procedures are available. Separate solutions of oxidant and reductant prepared in deaerated samples of the same buffer as that contained in A can be added to A in measured amounts. This is called the method of mixtures. The reductant

can be added to A and titrated with an oxidizing agent, or the oxidant can be added to A and titrated with a suitable reducing agent. Let us titrate the reductant.

The indigo carmine is reduced by hydrogen and platinized asbestos. The reduced solution is then forced through a filter into a reservoir which has been washed with pure nitrogen and there residual hydrogen is blown out by a vigorous stream of nitrogen. From a burette B attached to this reservoir a measured quantity of the leuco indigo carmine is added to the buffer in vessel A. Burette B is then replaced by one containing K_3FeCy_6 and titration is begun with this deaerated ferricyanid solution while the solution is stirred either by the mechanical stirrer MP, shown in figure 1, or by the stream of nitrogen, I to O. After each addition of a fraction of the amount of oxidant required for complete oxidation the potential is observed until it becomes constant. Then the next portion of oxidant is added. Near the completion of the titration the increments of potential will become greater and the end-point is indicated by a comparatively large increment of potential induced by a small additional amount of ferricyanid. Having thus determined the total ferricyanid required for complete oxidation there can be calculated the percentage oxidation for each fractional part of this total.

In any such titration care must be taken that the potentials for significant ratios of reagent and its reductant, i.e., $\dfrac{\text{ferricyanid}}{\text{ferrocyanid}}$ do not lie in the region of potentials for significant ratios of $\dfrac{\text{oxidant}}{\text{reductant}}$ of the system under investigation.

Having determined by the procedure outlined above the variation of potential with variation in the ratio of reductant to oxidant at constant pH, the experiment can be repeated in buffers of different pH. Or there can be added to buffers of different pH a fixed mixture of oxidant and reductant. This second set of experiments reveals the effect of variation of pH at constant ratio of oxidant to reductant.

It is sometimes advantageous to employ a hydrogen electrode in the same buffer mixture as that employed for the oxidation-

reduction system and to substitute this for the calomel half-cell C. We shall see in the next section the conditions under which such a chain gives the same E.M.F. independent of the buffer used.

It is significant that in practically all the cases examined the same results have been obtained with electrodes of platinum, gold, gold-plate, thin coats of platinum deposited on glass, "rhotanium" alloy and pure mercury. However, slight differences between electrodes of the same material are sometimes found and it is always best to use two.

The vessel A and calomel half-cell C are arranged so that they can be immersed in a constant-temperature oil-bath and are rigidly joined to the same support HD to lessen the danger of disturbing the liquid-junction in S.

If the liquid-junction can be made in a reproducible manner it is safe to neglect the small, residual potential-difference since it cancels in most of the comparative data.

There being no way to measure directly the pH of buffer + dye, the dye and titrating agent are kept at very low concentration in solutions of the same buffer composition and the pH of this buffer as measured with the hydrogen electrode is assumed to be the same as the mixture with corrections which can be made when the dissociation constants of the added materials have been determined.

Potential differences are measured with a potentiometer. Standards and precautions are discussed in The Determination of Hydrogen Ions (Clark, 1922) and in other texts.

EQUATIONS AND SOME TYPICAL APPLICATIONS

For the sake of conciseness it will be well to maintain a uniform procedure in developing the equations we shall have to employ. Several devices are now in use. They all lead to the same final working equations. This is evidence not only of lack of agreement upon an explanation of electrode mechanism but also of the fact that the devices postulated are to the actual mechanism like a convenient staging to the survey and construction of a building. When the final equations are built the staging disap-

pears. There is left a structure of thermodynamic relations but their verification tells nothing *directly* of the mechanisms involved.

For this reason some writers prefer to throw the components of a cell reaction directly into an electromotive force equation; but postulated mechanisms still have their uses.

Recognizing this it has seemed to me that the procedure outlined in the second edition of The Determination of Hydrogen Ions, chapter 16 (Clark 1922)[1] is somewhat more useful to the present purposes than some of the other procedures since it involves a device of considerable aid to the maintenance of orientation amid the complexities to be encountered.

We shall assume that in formulating the equilibrium state of an oxidation-reduction system we can include an electron activity a_{es} as in equation (1).

$$a_{es}^n = K \frac{a_r}{a_o} \tag{1}$$

Here n is the number of electrons required for the transformation of oxidant of activity a_o to reductant of activity a_r.

Let us now immerse an electrode, the material of which (e.g., platinum) does not readily enter into equilibrium with the materials of the solution. If a_{em} is the intrinsic electron activity of the "unattackable" electrode, there will be established a difference of potential E between electrode and solution in accordance with the equation

$$E = C - \frac{RT}{F} \, ln \frac{a_{es}}{a_{em}}$$

Ignoring the complex problem (involving the Volta effect) of why it is that the equations applicable to working conditions make it *appear* as if a_{em} were a constant, let us so regard it. Then

$$E' = C_2 - \frac{RT}{F} \, ln \, a_{es} \tag{2}$$

Equation (2) we shall call our fundamental electrode equation.

[1] Compare Clark and Cohen, 1921 and 1923.

Substituting (1) in (2) we have

$$E = C_3 - \frac{RT}{nF} \, ln \, \frac{a_r}{a_0} \tag{3}$$

Equation (3) with an important interpretation presently to be noted is the general form for an oxidation-reduction system; but we must now adopt a standard of reference for electrode potential-difference. That of the so-called normal hydrogen electrode will be used.

Applying (1) to the reaction $2H^+ + 2e \rightleftharpoons H_2$ and substituting in (2) we have

$$E = C_4 - \frac{RT}{F} \, ln \, \frac{\sqrt{a_{H_2}}}{a_{H^+}}$$

or using hydrogen pressure, P,

$$E = C_5 - \frac{RT}{F} \, ln \, \frac{\sqrt{P}}{a_{H^+}}$$

By definition in the commonly accepted convention regarding the normal hydrogen electrode, $E = 0$ when $P = 1$ atmosphere and $a_{H^+} = 1$. (The normal hydrogen electrode.)

Then C_5 is zero and the cell

normal	‖	oxidant	
hydrogen	‖		Pt
electrode	‖	reductant	
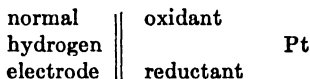
has an E.M.F. equal to E of equation (3).

We shall consistently use the normal hydrogen electrode standard of reference, and shall designate single potential-differences so referred by the symbol E_h.

In giving signs to single potential-differences we shall call a single potential difference " + " when, if the half-cell A involved were joined by liquid junction to a normal hydrogen electrode half-cell, the metal of the half-cell A would appear to be positive to the metal of the normal hydrogen electrode.

Now having chosen, for purposes of schematic presentation, to

orient the relation of reductant to oxidant as a difference of electrons we shall have to be consistent, and when dealing with particular cases in which we employ oxidants and reductants which can dissociate we shall have to carefully identify the species used as oxidant and reductant in equation (3).

There are many possible cases, as

$$Ox + e \rightleftharpoons \overline{Red}$$
$$\overset{+}{Ox} + 2e \rightleftharpoons \overline{\overline{Red}}$$
$$Ox + 2e \rightleftharpoons \overline{\overline{Red}}$$

etc.
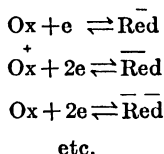
In the last case we identify the reductant as the anion of a diacidic acid. Such identification is the key to the formulation of effects due to alteration of hydrion activity.

To simplify the next steps we shall temporarily regard activities to be proportional to concentrations. Thus, if we continue with the case under discussion we have:

$$E_h = C - \frac{RT}{nF} \ln \frac{[\overline{\overline{Red}}]}{[Ox]} \qquad (4)$$

Also we have the sum (5) of all forms of reductant and the dissociation equilibrium equations (6) and (7).

$$[S_r] = [\overline{\overline{Red}}] + [H\overline{Red}] + [H_2Red] \qquad (5)$$

$$\frac{[H\overline{Red}] [H^+]}{[H_2Red]} = K_1 \qquad (6)$$

$$\frac{[\overline{\overline{Red}}] [H^+]}{[HRed]} = K_2 \qquad (7)$$

Combining (5) (6) and (7) and substituting in (4) we obtain (8) where constants that can properly be assembled are united in E_o.

$$E_h = E_o - \frac{RT}{2F} \ln \frac{[S_r]}{[S_o]} + \frac{RT}{2F} \ln [K_1K_2 + K_1 [H^+] + [H^+]^2] \qquad (8)$$

In (8) we have let $[S_o]$, the concentration of total oxidant, be identical with [Ox] of (4).

A series of similar hypothetical cases with their characteristic last terms are tabulated and illustrated by Clark and Cohen (second paper, Studies on Oxidation-Reduction).

Equation (8) shows clearly the conditions for experimental segregation of the effects of the independent variables. If

TABLE 1

Titration of leuco o-cresol-indophenol with ferricyanid at pH 8.65. 30°.

K_3FeCy_6	OXIDATION	$0.03006 \log \frac{[S_r]}{[S_o]}$	Eh OBSERVED	E'o	E'o CORRECTED	DEVIATION FROM +0.0837
cc.	*per cent*		*volts*			
1	4.31	+0.0405	+0.0432	+0.0837	0.0836	−0.0001
2	8.62	+0.0308	0.0526	0.0834	0.0833	−0.0004
3	12.93	+0.0249	0.0587	0.0836	0.0834	−0.0003
4	17.24	+0.0205	0.0633	0.0838	0.0835	−0.0002
5	21.55	+0.0169	0.0671	0.0840	0.0836	−0.0001
6	25.86	+0.0137	0.0702	0.0839	0.0835	−0.0002
7	30.17	+0.0110	0.0732	0.0842	0.0836	−0.0001
8	34.48	+0.0084	0.0759	0.0843	0.0836	−0.0001
9	38.79	+0.0059	0.0785	0.0844	0.0836	−0.0001
10	43.10	+0.0036	0.0809	0.0845	0.0837	0.0000
11	47.42	+0.0014	0.0834	0.0848	0.0839	+0.0002
12	51.73	−0.0009	0.0858	0.0849	0.0839	+0.0002
13	56.04	−0.0032	0.0882	0.0850	0.0839	+0.0002
14	60.35	−0.0055	0.0904	0.0849	0.0837	0.0000
15	64.66	−0.0079	0.0929	0.0850	0.0837	0.0000
16	68.97	−0 0104	0.0955	0.0851	0.0838	+0.0001
17	73.28	−0.0132	0.0984	0.0852	0.0838	+0.0001
18	77.59	−0.0162	0.1016	0.0854	0.0840	+0.0003
19	81.90	−0.0197	0.1054	0.0857	0.0842	+0.0005
20	86.21	−0.0240	0.1097	0.0857	0.0841	+0.0004
21	90.52	−0.0295	0.1154	0.0859	0.0843	+0.0006
22	94.83	−0.0380	0.1242	0.0862	0.0845	+0.0008
23	99.14	−0.0620	0.1486	0.0866	0.0848	+0.0011
23.2	100					

oxidant and reductant are kept at such low concentration that they have a negligible effect upon the hydrion concentration of a buffer solution, and if [H+] is kept at a definite value by this buffer solution, the last term of equation (8) becomes a constant for the given condition and (8) becomes (9).

$$E_h = E_o' - \frac{RT}{2F} \ln \frac{[S_r]}{[S_o]} \qquad (9)$$

For example, Cohen, Gibbs and Clark (1924) give the data of table 1 for the titration with ferricyanid of leuco o-cresol indophenol. The temperature was 30° and hence equation (9) becomes

$$E_h = E_o' - 0.03006 \log \frac{[S_r]}{[S_o]} \qquad (10)$$

Since in this case, even with buffer, there is an appreciable change of acidity during the transformation, there is applied in the next to last column of table 1 a correction experimentally determined. The resulting constant is quite satisfactory as shown by the deviations in the last column of table 1.

LaMer and Baker (1922) have published some accurate data for cases to which equation (9) applies. Their data illustrated by figure 10, page 164 will be referred to again. Another illustration of the typical curves given by equation (10) are shown in figure 2, together with experimental data for three of the indigo sulphonates studied by Sullivan, Cohen and Clark (fourth paper, Studies on Oxidation-Reduction). In this figure the curve for the monosulphonate was located by means of experimental data obtained at other values of pH.

These cases will suffice to show the conformity of experimental data with equation (9) which is applicable only when the hydrion concentration is constant.

We shall next consider the methods of completing the data for equation (8) which involves the variable $[H^+]$.

In equation (8) if $\frac{[S_r]}{[S_o]} = 1$ we have (11).

$$E_h = E_o + \frac{RT}{2F} \ln [K_1 K_2 + K_1 [H^+] + [H^+]^2] \qquad (11)$$

But we have already seen that at any particular value of $[H^+]$ the mid-point of a titration curve is the condition that $\frac{[S_r]}{[S_o]} = 1$. Consequently by repeating the first series of measurements in
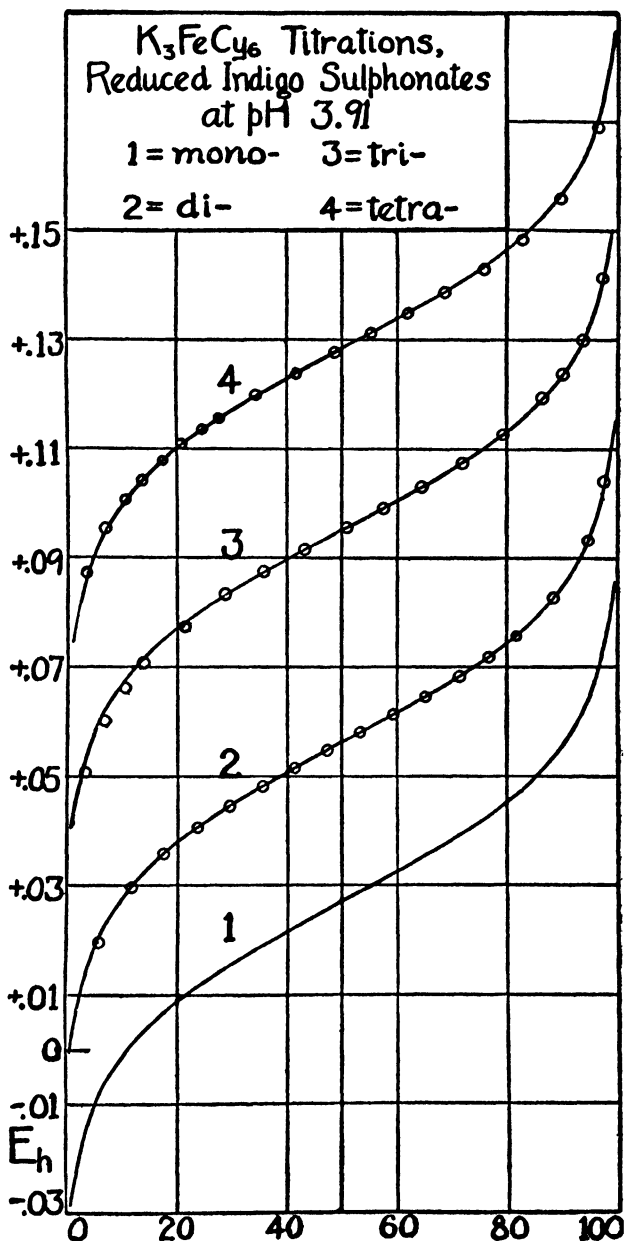
FIG. 2. RELATION OF ELECTRODE POTENTIAL, E_h (ORDINATE) TO PERCENTAGE OXIDATION (ABSCISSA)

buffers of different hydrion concentration we obtain the data to solve (11). Involving fewer sources of experimental error is the method in which a *fixed* mixture of total reductant and

$$E_h = E_o - .0295 \log \frac{S_R}{S_o} + .0295 \log \left[K_1 K_2 + K_1 [H] + [H]^2 \right]$$

$$E_h = E_o + .0295 \log [H]^2$$

$$E_h = E_o + .0295 \log [K_1 [H]]$$

$$E_h = E_o + .0295 \log K_1 K_2$$
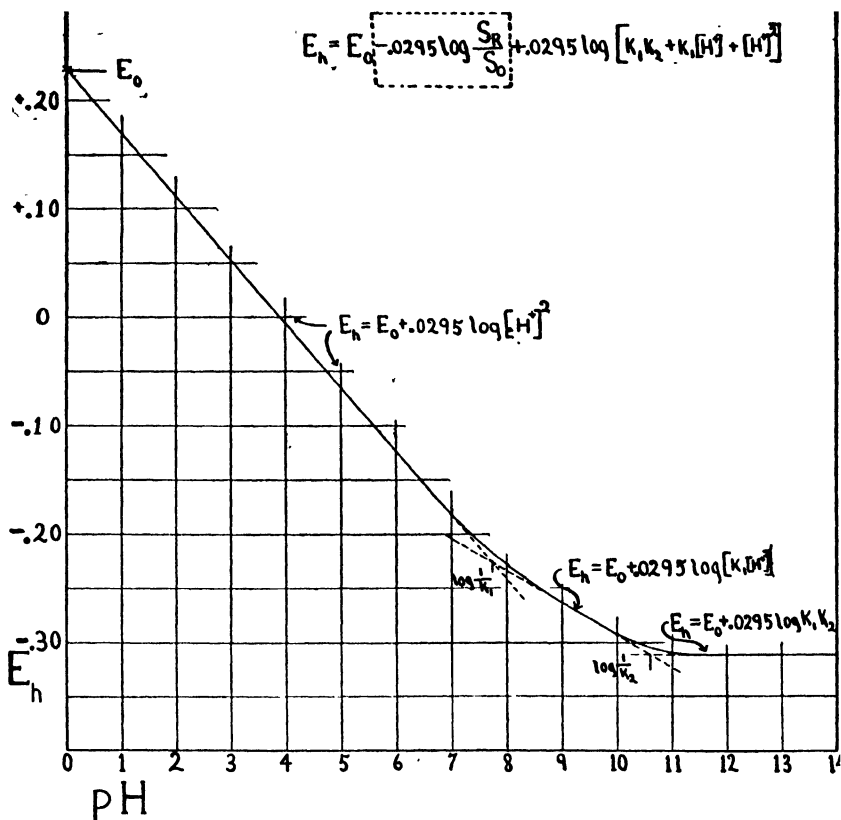
FIG. 3. VARIATION OF POTENTIAL WITH pH WHEN TOTAL OXIDANT AND TOTAL REDUCTANT ARE KEPT CONSTANT AT $\frac{S_r}{S_o} = 1$

Anthraquinone, 2,7-disulphonic acid and its reductant at 25°

oxidant is added to a series of buffers of various pH values.   This fixed mixture need not be that of $\frac{[S_r]}{[S_o]} = 1$ since the previous set of measurements has determined E_o' for a given value of $[H^+]$. It is necessary, however, for the purpose of orientation, that this

second set of measurements include one in which $[H^+]$ is the same as in the first set.

If now either K_1 or K_2 comes within the experimental range of $[H^+]$ it can be measured. This is best shown graphically by figure 3 drawn with the aid of data for $25°$ on anthraquinone, 2,7-disulphonic acid supplied by Conant, Kahn, Fieser and Kurtz (1922).

These authors give $K_1 = 2 \times 10^{-8}$ and $K_2 = 3 \times 10^{-11}$. It is obvious that at high values of $[H^+]$ (low pH) both K_1K_2 and $K_1 [H^+]$ are negligible. Consequently the curve has a slope $\dfrac{-dE}{dpH} = 0.059$. When $[H^+] = K_1$ and $\log \dfrac{1}{K_1} = pH$, the curve is midway in its inflexion to the section where K_1K_2 and $[H^+]^2$ are negligible compared with $K_1 [H^+]$. Consequently the slope characteristic of this section is $\dfrac{-dE}{dpH} = \dfrac{0.059}{2} = 0.0295$.

When $[H^+] = K_2$ and $\log \dfrac{1}{K_2} = pH$ the curve is midway in its inflexion to the section where $K_1[H^+]$ and $[H^+]^2$ are negligible compared with K_1K_2. There $\dfrac{-dE}{dpH} = 0$.

Conversely the intersections of projections of the several sections of the curves fall at pH values corresponding numerically with what are called the pK_1 and pK_2 values, namely and respectively $\log \dfrac{1}{K_1}$ and $\log \dfrac{1}{K_2}$.

In figure 4 are the $E_o':pH$ curves of the indigo sulphonates for which the $E_h:\%$ oxidation curves are shown in figure 2. Some discrepancies to be noted in the more alkaline solutions were traced to a specific effect of borate buffers. (See the original paper.)

It will be noted that within the experimental range of pH covered by the curves for the sulphonated anthraquinone and the sulphonated indigos there is no sign of the influence of dissociation in the sulfonic acid groups. This is chiefly because no acidic group which is *common* to both oxidant and reductant makes its presence felt in such $E_o':pH$ curves *unless* the "strength" of this

group *changes* in the transformation of oxidant to reductant. In case this change does occur the equation can easily be developed by consistently following the plan outlined. (See Clark and Cohen, 1923.)

Relation of E'_0 to pH

1 = Monosulphonate of Indigo
2 = Disulphonate   "   "
3 = Trisulphonate   "   "
4 = Tetrasulphonate   "   "
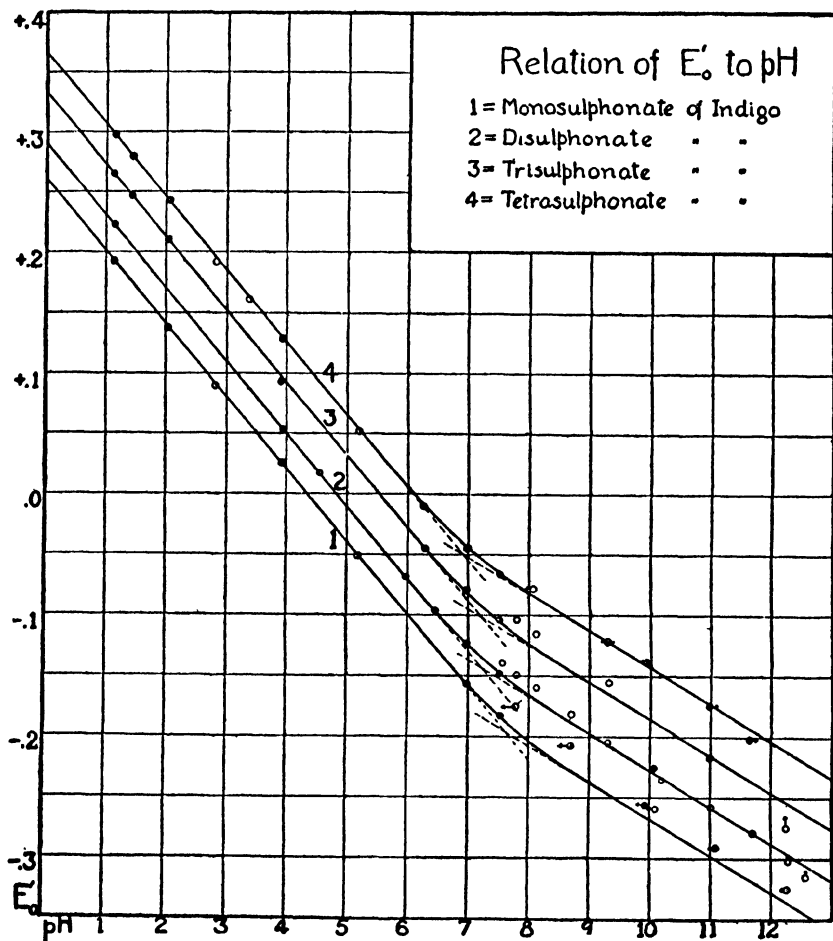
FIG. 4

Specific instances of this occurrence are found among the indophenols. For instance in the oxidant (I) and the reductant (II) of the methyl indophenol,

$$HO \langle\!\!\!\bigcirc\!\!\!\rangle N = \overset{CH_3}{\langle\!\!\!\bigcirc\!\!\!\rangle} = O \qquad (I)$$

$$HO \langle\!\!\!\bigcirc\!\!\!\rangle \overset{H}{N} \overset{CH_3}{\langle\!\!\!\bigcirc\!\!\!\rangle} OH \qquad (II)$$
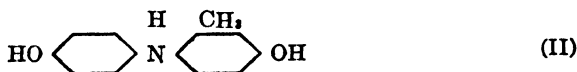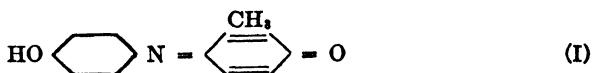
the dissociation constant of the common phenolic group shifts in value and there has to be taken into account both K_o of the oxidant and K_r of the reductant each applying to the same structural group. The displacement E-C and the intersections of
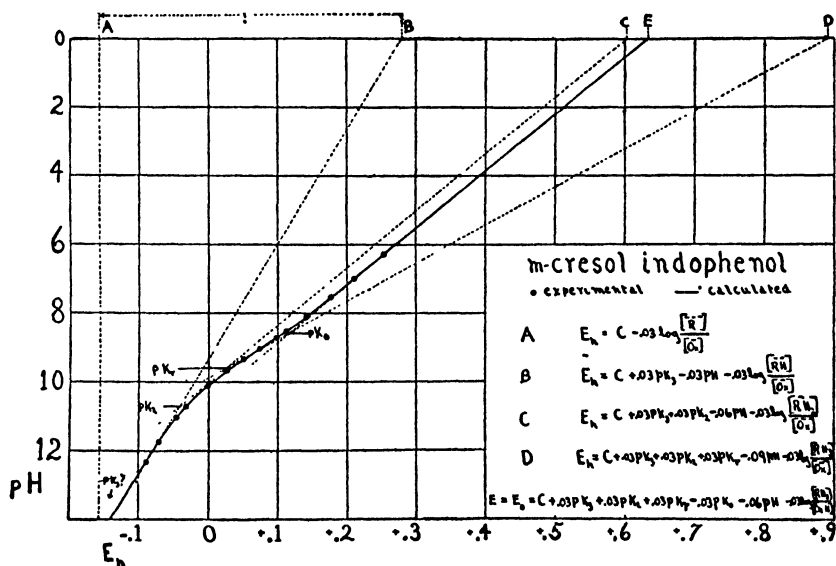
FIG. 5

D, E and C illustrated in figure 5 are used to determine the values of these constants.

In the case of the systems now under discussion the absence of any zero value for $\dfrac{-dE}{dpH}$ indicates that one hydrogen is fixed—presumably that on the bridging N of the reductant (II). Neglecting the inappreciable value of this dissociation and developing the equation in accordance with the scheme previously outlined we have, at the temperature (30°) of the measurements,

equation (12) in which K_o is the dissociation constant of the oxidant, K_r the dissociation constant of the same group as it occurs in the reductant and K_2 is the dissociation constant of the phenolic group created by reduction.

$$E_h = E_o - 0.03006 \log \frac{[S_r]}{[S_o]} + 0.03006 \log [K_r K_2[H^+] + K_r[H^+]^2 + [H^+]^3]$$

$$- 0.03006 \log [K_o + [H^+]] \tag{12}$$

With the values

$$K_o = 2.8 \times 10^{-9}$$
$$K_r = 2.7 \times 10^{-10}$$
$$K_2 = 2.2 \times 10^{-11}$$
$$E_o = + 0.632$$

there is found the curve as drawn in figure 5. With this, the experimental data are shown to agree very well.

In this curve there are four sections for which the determining values of $\frac{-dE}{dpH}$ are in order from low to high pH:0.06, 0.09, 0.06, and 0.03. The "0.09-slope" is not very distinct in this instance but is very distinct in the case of 2.6-dibromophenol indophenol.

With the constants characteristic of the 2.6-dibromophenol indophenol system Cohen, Gibbs and Clark (1924) have constructed the isometric figure 6 which illustrates the type of surface determined by equation (12).

The recognition of details such as those which reveal the "0.09-slope" in the indophenol system, and the use of a consistent method of formulating equations have been imperative prerequisites to the full appreciation of such remarkable cases as that of the methylene blue-methylene white system.

Here as shown by the E'_o:pH curve of figure 7 we have a situation which seems at first very difficult to analyze. However, with help from structural chemistry a satisfactory formulation is reached directly.

The Bernthsen formula for methylene blue is supported by a very beautiful series of syntheses. If we write it with con-

ventional symbols for electronic configuration (figure 8) pre-
serving the rule of eight and the rule of two (see Lewis, 1923)
we observe that one of the terminal nitrogens in the oxidant
should be "polar" and comparable with that of a substituted
ammonium.
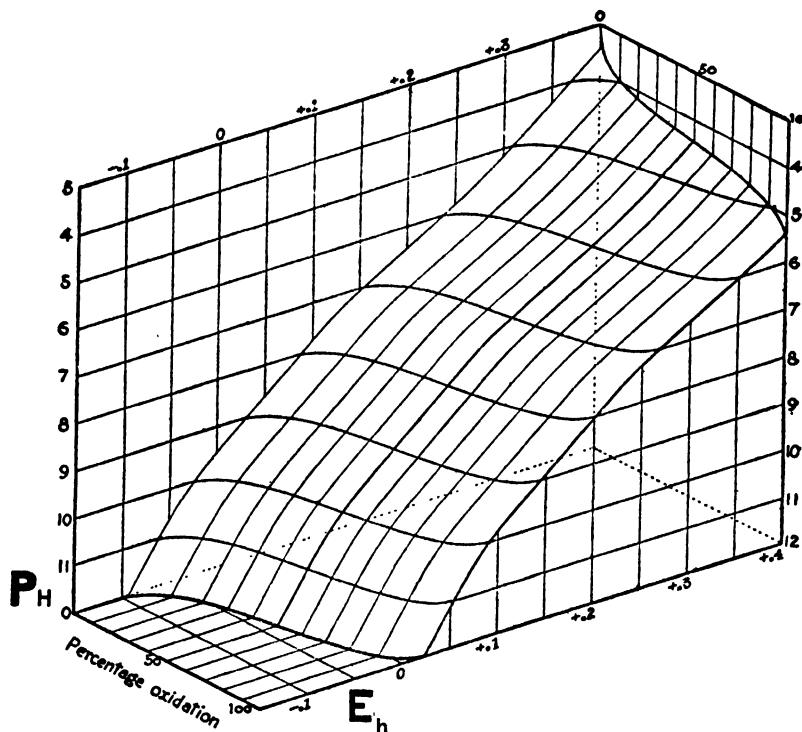
Fig. 6. Isometric Drawing of the Surface Descriptive of the System Com-
posed of 2–6 Dibromophenol-indophenol and Its Reductant and [H⁺] at
Different Values of pH

Now for the unmethylated analogue of methylene blue, Lauth's
violet, we find an inflexion of the E_o':pH curve at pH $=$ 11
(see fig. 7) indicating a strong basic group, $K_b = 10^{-3}$. By
analogy with substituted ammoniums we should expect the

introduction of methyl groups to increase the "strength" of the base. In methylene blue no inflexion of the E_0:pH curve occurs
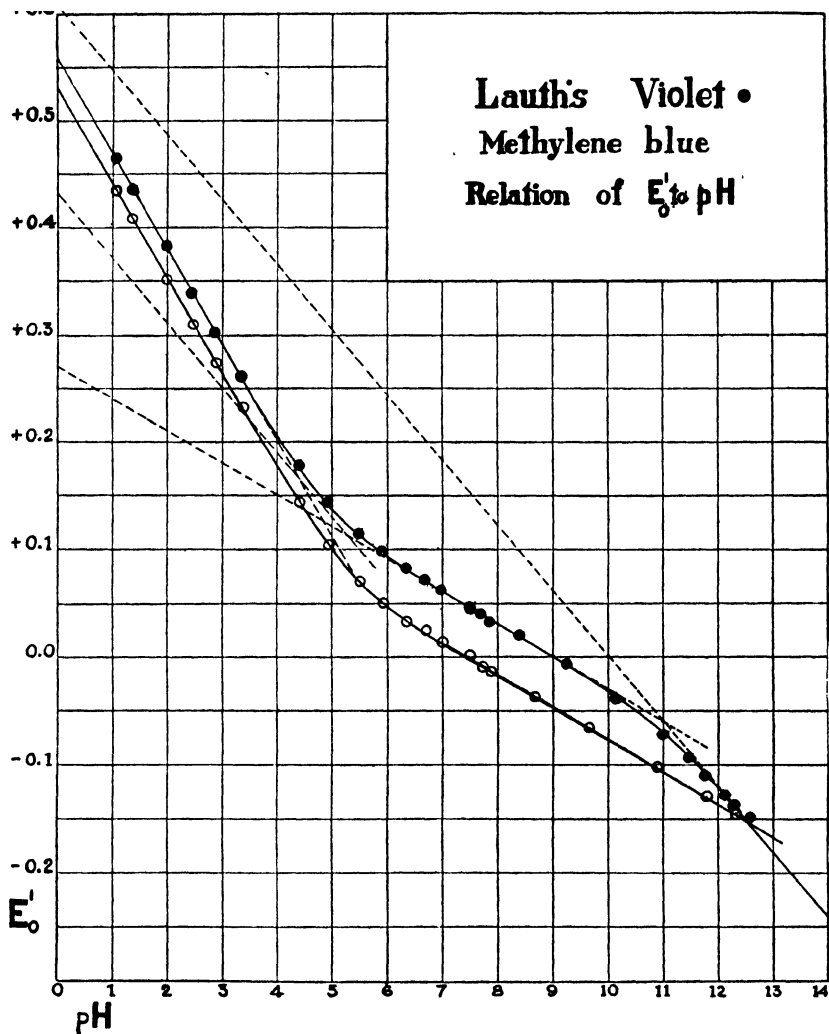
FIG. 7

in the alkaline regions studied. If our reasoning is correct this experimental fact means that methylene blue base is comparable in "strength" to an alkali hydroxide and since the chloride suffers

no hydrolysis within the range of pH used, the constant eludes measurement. Abundant supplementary evidence of this is to be found in the literature.

Clark, Cohen and Gibbs (1925) starting with this interpretation and the orienting reaction

$$\text{Oxidant}^{+}\text{ cation} + 2e \rightleftarrows \text{Reductant}^{-}\text{ anion}$$
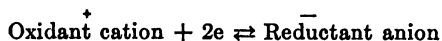
were led, by the procedure described, directly to a satisfactory equation (see original paper) in accordance with which the curves of figure 7 are drawn.

Briefly the interpretation is as follows. The polar group of methylene blue is so strong that its K_b value is not measured; that of Lauth's Violet has a K_b value of 1.89×10^{-3} (inflexion
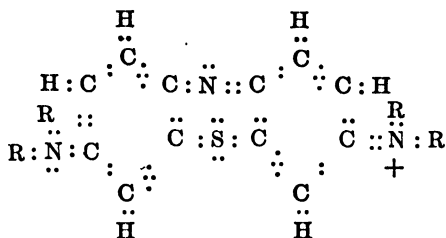
FIG. 8. CONVENTIONAL ELECTRONIC STRUCTURE OF A THIAZINE

at pH 11). The opposite dimethylamino group of methylene blue and amino group of Lauth's violet is each so weak that its K_b value is not measured. The convenient form of the reaction given above indicates that the reductant is an anion. At the point concerned, which may be assumed to be the bridging nitrogen, a hydrogen ion is bound so firmly that there is established a lower limit of 0.03 for $\dfrac{-dE}{dpH}$. At the same time the reduction, by destroying the polarity of the strong basic group has turned it into an ordinary substituted amino group which acquires weak basic properties either by addition of H^+ or by hydration and dissociation of $O\overline{H}$. The now symmetrically placed, substituted amino group common to oxidant and reductant has become of appreciable basic strength. These changes

listed in table 2, establish the not unique "0.09-slope" over a remarkably wide zone of pH.

These few illustrative examples have been treated in some detail in order to emphasize several matters of considerable importance.

In the first place it is the detailed working out of such specific cases that is a necessary prerequisite to the mastering of more difficult problems which are continuously arising.

In the second place it is alone the charting of specific cases that can give us a proper appreciation of the remarkable way in which alteration of pH affects the relation of one system to another.

TABLE 2

Ionization constants, centers of inflexion of $E_0':pH$ curves and characteristic potentials of Lauth's violet- and methylene blue systems at 30°

GROUP	LAUTH'S VIOLET		METHYLENE BLUE	
	Basic constant	Inflexion at pH	Basic constant	Inflexion at pH
Oxidant's polar.................	1.9×10^{-3}	11.0	Too high to measure	None
Oxidant's amino.................	Negligibly small	None	Negligibly small	None
Reductant's bridging N.........	Fixes H^+	None	Fixes H^+	None
Reductant's first amino........ .	3.8×10^{-9}	5.30	1.35×10^{-8}	5.85
Reductant's second amino......	4.5×10^{-10}	4.38	6.3×10^{-10}	4.52
E_0', potential at pH = 0........	+0.563		+0.532	

It has not yet been made clear to many writers that certain statements regarding the effect of acid or alkali upon oxidation-reduction can have no meaning unless the systems concerned are specified. Several well defined cases are now known in which one system having a reducing potential relative to a second system becomes oxidative with respect to the second on change in the pH of the solution and subsequently reductive again on further change in pH.

Third, the details reveal characteristic constants for each system and these are valuable in quantitative studies on substitution as will be shown in a later section.

DATA ON ENERGY CHANGES

It is well known that potentiometric measurements, when applicable, furnish precise data for certain energy changes.

Free energy changes involved in the organic reactions now under review are implicit in the equations we have been discussing. For instance let equation (8) be recast to the following form.

$$2FE_h = 2FE_o - RT \, ln \, \frac{[S_r]}{[S_o]} + RT \, ln \, [K_1K_2 + K_1 \, [H^+] + [H^+]^2]$$

If K_1 and K_2 are small in relation to $[H^+]$ and if $[H^+] = 1$

$$2FE_h = 2FE_o - RT \, ln \, \frac{[S_r]}{[S_o]}$$

Since the use of E_h values implies the coupling of the half-cell with that of the normal hydrogen electrode, $2FE_h$ is the yield of free energy, or $- \Delta F$ in volt-coulombs, of the reaction:

Oxidant (1 molar) $+$ H_2 (1 atmos) $\rightarrow$ Hydrogenated Reductant (1 molar)
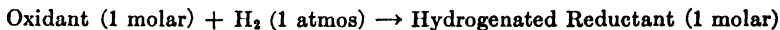
Thus in the case of indigo carmine $E_o = + 0.291$ and consequently if the reaction proceeds in the direction indicated above there would be yielded under conditions of maximum work the free energy of 56.16 kilo joules or 13.413 mean gram calories.

When K_1 and K_2 are large in relation to $[H^+]$ and $\frac{[S_r]}{[S_o]} = 1$

$$2FE_h = 2FE_o + RT \, ln \, K_1K_2$$

Thus in the case of anthraquinone 2, 7-disulphonic acid (see figure 3), Conant, Kahn, Fieser and Kurtz (1922) give

$$K_1 = 2 \times 10^{-8} \quad K_2 = 3 \times 10^{-11} \quad \text{and } E_o = 0.229 \text{ at } T = 298$$

Hence RT $ln \, K_1K_2 = -103.9$ kilo joules, and $2FE_o = 44.2$ kilo joules.

Consequently the cell made up of the hydrogen half-cell and the oxidation-reduction half-cell (liquid-junction potential-differences being neglected) would run of itself in the direction

Oxidant (1 molar) + H_2 (1 atmos) → Hydrogenated Reductant (1 molar)

at $[H^+] = 1$ yielding 44.2 kilo joules; and in the opposite direction, namely

Reductant anion (1 mol) + $2H^+$ (2 mols) → Oxidant (1 molar)
+ H_2 (1 atmos)
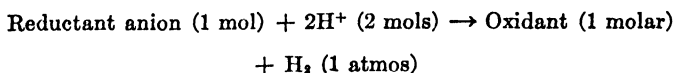
when the oxidant and reductant are at high alkalinities then yielding 59.9 kilo joules.

There are valuable additional data which may be gained from a study of temperature effects. If the increase of potential with increase of temperature $\dfrac{dE_o}{dT}$ is determined, the Gibbs-Helmholtz equation,

$$- \Delta H = 2FE_o - 2FT \frac{dE_o}{dT}$$

permits the calculation of the total energy change $-\Delta H$ and the latent heat

$$- T \frac{d(\Delta F)}{dT}.$$

Biilmann (1920) has thus found the total energy change for the hydrogenation of benzoquinone and toluquinone, Biilmann and Lund (1923) for the hydrogenation of alloxan and Conant and Fieser (1922) for several anthraquinones, naphthoquinones and quinones. The last authors find that, while anthraquinones differ markedly from quinones and naphthoquinones in their values of ΔF and ΔH, the latent heats of reduction are of the same order of magnitude for all of these systems.

There are thus being accumulated some fundamental data on energy relations which are far more precise than some of the existing thermal data. Incidentally we might note that the variation of free energy change with variation of the pH of the solution could not have been very easily taken into consideration in certain of the older types of measurement. The potentiometric methods reveal free energies of ionization and dilution of H^+

which are implicit in the equations given above but which have not been detailed in this brief sketch.

NEW METHODS OF DETERMINING pH

Any of the systems we have been considering may be used under proper conditions to determine pH. Consider for instance any case for which equation (8) holds.

$$E_h = E_o - \frac{RT}{2F} \ln \frac{[S_r]}{[S_o]} + \frac{RT}{2F} \ln [K_1K_2 + K_1 [H^+] + [H^+]^2] \qquad (8)$$

Let the ratio $\frac{[S_r]}{[S_o]}$ be unity and let attention be confined to the zone of hydrion concentration where $[H^+]$ is large in relation to K_1 and K_2. Then

$$E_h = E_o + \frac{RT}{F} \ln [H^+]$$

or at 20°,

$$pH = \frac{E_o - E_h}{0.058}$$

Now quinhydrone in acid solution fulfills the conditions. The dissociation constants of hydroquinone are very low and are for present purposes negligible. The hydroquinone and quinone resulting from the dissociation of quinhydrone are fixed in ratio. Consequently $\frac{[S_r]}{[S_o]}$ is established. Furthermore air oxidation is slow in acid solution.

Developing his equations from a different point of view Biilmann (1920) realized the implications above described and devised his so-called quinhydrone electrode for the determination of pH. It is a very simple arrangement. A little solid quinhydrone is mixed with the solution to be tested and placed in a vessel such as is used for a calomel half-cell. A bright platinum electrode is then dipped into the mixture and liquid junction is made with a standard half-cell. Knowing the value of this standard and having measured the E.M.F. of the chain,

E_h is found at once.   Then since E_o has already been established pH is determined.

The following are values of E_o at different temperatures:

AUTHOR	TEMPERATURE	E_o
Biilmann and Krarup (1924)	0	0.717
Conant and Fieser (1922)	0	0.713
Biilmann (1920)	18	0.704
Veibel (1923)	18	0.704
Biilmann (1920)	25	0.699
LaMer and Baker (1922)	25	0.699
Biilmann and Krarup (1924)	37	0.690
Conant and Fieser (1922)	40	0.682

Biilmann and Krarup propose the equation

$$\pi_r = 0.7175 - 0.00074t$$

where π_r is the value of our E_o at temperature t.

One advantage of the quinhydrone electrode is the rapidity with which the equilibrium potential is attained.   Another advantage over the classic hydrogen electrode is this: The finely divided metal (platinum or palladium black) necessary to the operation of the hydrogen electrode is easily "poisoned" by many substances or else will so catalyze the reduction of a substance as to alter the system under study.   In the quinhydrone electrode the hydrogen and the finely divided catalyst are eliminated.   Its potential adjusts rapidly, very often much more rapidly than certain classes of reagents affect the constituents of the oxidation-reduction system.   Consequently it is possible to use the quinhydrone electrode in solutions incompatible with the hydrogen electrode and even in systems which will ultimately oxidize hydroquinone.   For instance Biilmann (1921) has employed it in dilute solutions of nitric acid, fumaric acid, etc., and a number of other investigators have found it useful in a variety of instances. (Compare Bodforss, 1922; Schreiner, 1922–1924; Larsson, 1922; Pring, 1924; Kolthoff, 1923; Harris, 1923; Darmois and Honnelaitre, 1924; Hugonin, 1924.)   It has also been applied to the measurement of pH in soils (Biilmann, 1924) in milk (Lester, 1924) in beer (Kolthoff, 1923).

Its limitations in alkaline solution are two-fold. As equation (8) (page 136) will indicate, corrections have to be made for dissociation of hydroquinone. See LaMer and Parsons (1923). More serious is the oxidizing effect of air. LaMer and Rideal (1924) have made an interesting study of this. Compare Meunier and Queroix (1924).

Perhaps at this point it may be well to add a note to this subject. It is very proper that investigators who have dealt with organic systems have attempted to maintain conditions for constancy of electrode potential-differences over long periods of time. Thus Granger's dissertation presents an admirable study of long-time experiments on the quinhydrone electrode. On the other hand the evidence is growing that many of the organic systems, such as the quinone-hydroquinone system, give their significant and reproducible potentials much more rapidly than students of the hydrogen electrode and of metal electrodes are accustomed to, and that subsequent changes of potential are due to decompositions the effects of which should not be allowed to cloud the main issue. Now, while no one would care to depend in important cases upon initial potentials which immediately begin to drift, I would like to call attention to the fact that reasonable measurements in alkaline solutions may be made by first de-aerating the solution, then adding the quinhydrone as a small amount of saturated solution and taking the initial potentials. Incidentally I have made fair estimates of the dissociation constants by this procedure.

In acid solutions the quinhydrone electrode has a good stability and Veibel (1923) has proposed its use as a standard which he finds to be as reproducible as his 3.5 N-calomel electrodes and more reproducible than his 0.1 N-calomel electrodes. On the other hand Sørensen and Linderstrøm-Lang (1924) have pointed out that since the permanence of the quinhydrone electrode is not equal to that of the calomel electrode the latter should remain standard.

In any case where the quinhydrone or a similar electrode is used to determine pH there must be taken into consideration the so-called "salt-effects." Because of its theoretical importance

the salt-effect will be discussed in a separate section where treatment of the quinhydrone electrode will be continued.

<center>EFFECTS OF SALT AND SOLVENT</center>

It will have been noticed that in developing equations used to outline the main features of the subject we assumed that the ratio between activity of oxidant and activity of reductant could be replaced by the ratio of the concentrations. This distinctly limited the treatment to a first approximation. If persisted in, certain effects would be classified as "salt-errors."

Sørensen, Sørensen and Linderstrøm-Lang (1921) have examined such "errors" in the case of the quinhydrone electrode.

If we assume for simplicity that the quinhydrone electrode is being operated at constant hydrion activity in acid solution we have the equation

$$E_h = E_o - \frac{RT}{2F} \, ln \, \frac{a_h}{a_q}$$

where a_h and a_q represent activities of hydroquinone and quinone respectively. Representing concentrations by C and activity coefficients by f we can write

$$E_h = E_o - \frac{RT}{2F} \, ln \, \frac{C_h f_h}{C_q f_q}$$

For the special case where $\dfrac{C_h}{C_q} = 1$ as determined by quinhydrone in absence of excess of either constituent the ratio $\dfrac{f_h}{f_q}$ determines the potential. But this ratio should be determinable by means of solubilities. This the Danish authors did obtaining a good correspondence between potentials found at different salt concentrations and that calculated with the aid of the solubility data on activity coefficients. Fortunately the effects of salt concentrations are not large until the salt concentration becomes large.

Linderstrøm-Lang (1924) has extended the work to a variety of salts and has charted certain corrections which are useful to those who apply the quinhydrone electrode in accurate determinations.

Bülmann and Lund (1921) applying the principles developed by Sørensen, Sørensen and Linderstrøm-Lang (1921) have used the so-called quino-quinhydrone and hydro-quinhydrone electrodes, in the one case the solution being saturated with quinone in addition to quinhydrone and in the other the solution being saturated with hydroquinone as well as with quinhydrone. These electrodes should be free from salt-effect because the solid phases establish a constant ratio of the activities of oxidant and reductant.

An interesting development in the same direction is found in an observation by Conant and Fieser (1923). They make use of the fact that tetrachlorobenzoquinone and its reductant do not form sufficient of the corresponding quinhydrone to prevent simultaneous saturation of solutions with oxidant and reductant. Now let us confine attention to acid solutions and the equation

$$E_h = E_o - \frac{RT}{2F} \ln \frac{a_r}{a_o} + \frac{RT}{F} \ln a_{H^+}$$

By the definition of activity the presence of the solid phases fixes the activities of the oxidant and reductant in the solvent independently of the nature of the solvent. Therefore

$$E_h = E_o' + \frac{RT}{F} \ln a_{H^+}$$

where E_o'' will vary with the solvent. If a fixed reference value of a_{H^+} were to be established for each solvent so that E_o'' for that solvent could be determined, we would have in the chloranil electrode a simple device for correlating experimentally the hydrogen ion activities of different solvents. Unfortunately there is as yet no perfectly satisfactory way of relating the hydrogen ion activity in one solution to that in another, but the time is not distant when the use of electrodes such as those here described will have developed for each of the more important solvents much more extensive data than we now possess.

Finally it may be suggested that the significance of the new developments lies not so much in the properties of a particular system as it does in the possibilities of devising, from the still

untouched stores of organic chemistry, systems adapted to special cases, and new experimental methods for the study of "salt-effects."

ANALYTICAL METHODS

The equations we have been using with the constants they involve are concise definitions of certain characteristics of each oxidation-reduction system. The establishment of these characteristics by accurate potentiometric measurements of pure compounds is the preliminary to an obvious method of later identification.

The analyst uses potentiometric methods to determine end-points in oxidation-reduction titrations; but if he confines his attention to end-points he may overlook valuable information furnished by a complete "titration-curve." In their study of the sulphonates of indigo, Sullivan, Cohen and Clark were able to establish fairly accurate characteristic constants for each system and consequently could predict the conduct of mixtures during titration. Thus they were able to approximately estimate by graphic methods the quantity of over-sulphonated or under-sulphonated indigo in some of their products. Even when the characteristic constants of a pure material have not been accurately established there may still be determined the order of magnitude of the percentage impurity provided this impurity is active. Thus in our recent studies at the Hygienic Laboratory we have established at least to our own satisfaction the presence of small percentages of active impurity in every sample of methylene blue at our disposal. Of course if an impurity is electromotively active in a zone of potential distinct from the zone characteristic of the chief constituent its detection is easy. Thus a titration of a commercial safranin with $TiCl_3$ revealed a large percentage of material active in a region very much more positive than the safranin itself.

The establishment of constants for a large number of different systems will give us not only data useful for identification but also a variety of titrating reagents from which to choose those suitable to specific purposes. When such a series of reagents is

assembled we shall have begun the systematization of oxidation-reduction titrations and can then carry over to this subject many of the principles developed by A. A. Noyes, Bjerrum and others for acidimetric and alkalimetric titrations.

Moreover, just as certain acid-base mixtures have characteristic pH values useful in tests of identity by the rapid colorimetric method of determining pH, so many oxidation-reduction systems have characteristic reduction intensities which would be measurable by a colorimetric method if we had a series of oxidation-reduction indicators.

The beginning of such a series will be described in the next section.

Another interesting application of potentiometric methods is in determining the ratio of oxidant to reductant during progressive changes. Thus, for example, Biilmann and Blom (1924) used this method in their determination of velocity constants of semidine or benzidine rearrangement, Clark, Cohen and Gibbs (1925) in following the photodynamic regeneration of methylene blue from methylene white, and Conant and Lutz (1923) in following the effect of irreversible upon reversible oxidation-reduction systems.

OXIDATION-REDUCTION INDICATORS

The detection of reduction by dye decoloration is a very old practice which was introduced to the chemist by the artisan of the indigo vat. Through histology came the indophenols and methylene blue. The latter has been used as an indicator of reduction in such a diversity of problems that it may be compared with litmus, the universal acid-base indicator of a now historic age.

Prior to Ehrlich's classic, *Das Sauerstoffbedürfniss des Organismus* (1885), little was known of any order for the reduction of the different dyes. Ehrlich's use of living tissues as supposedly graded, titrating reagents established a semblance of order and inspired a number of researches. The results might have been harmonious had it not been that reduction capacity, reduction intensity, equilibrium state and rate of reaction were jumbled in disharmony.
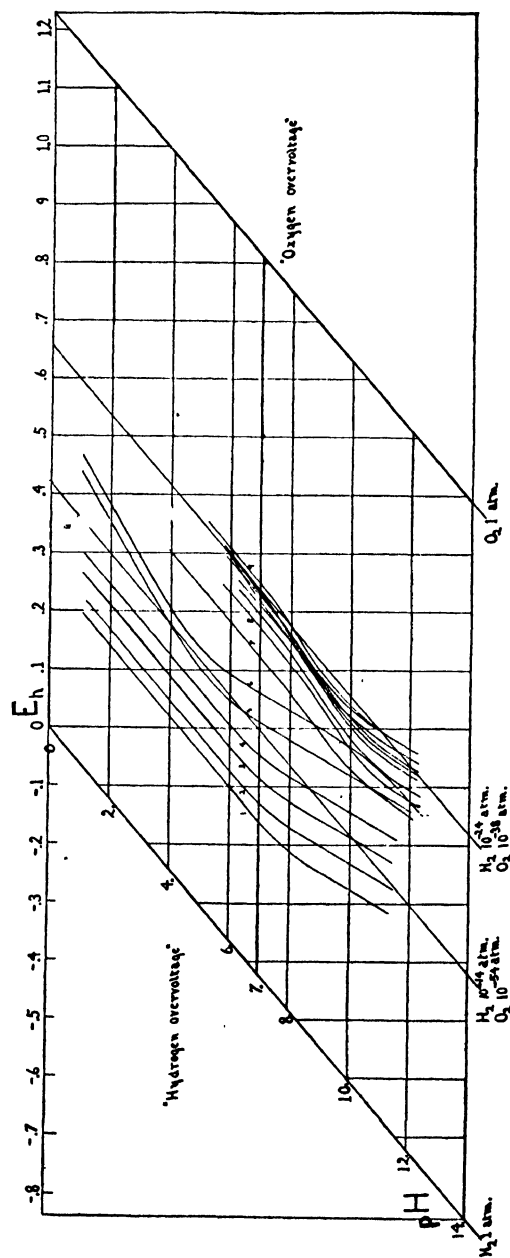
FIG. 9. E'_o:pH Curves of a Few Oxidation-Reduction Indicators

1. Indigo monosulphonate
2. Indigo disulphonate
3. Indigo trisulphonate
4. Indigo tetrasulphonate
5. Methylene blue
6. Lauth's violet
7. 1-naphthol 2-sulfonic acid indophenol
8-9. Indophenols

There is now little excuse for such confusion and with the potentiometric studies begun by Clark (1919) there is being built up a series of oxidation-reduction indicators suitable for the measurement of oxidation-reduction "intensity." These are comparable to the acid-base indicators used for the measurement of acid-base "intensity."

The methods employed have been described and data on such systems as those of the indigo sulphonates and methylene blue have been quoted. Therefore it remains for this section to summarize and to describe the chief features.

TABLE 3

Corrections to be applied to E_h as found on $E_0':pH$ curves to obtain E_h at given percentage reduction, 30°

REDUCTION	CORRECTION
per cent	*volts*
5	+0.038
10	+0.029
20	+0.018
30	+0.011
40	+0.005
50	0.000
60	−0.005
70	−0.011
80	−0.018
90	−0.029
95	−0.038

In figure 9 are shown the $E_0':pH$ curves of a few of the indicators studied in detail by the investigators at this laboratory.

Although it is practicable to present on one chart only a pair of the variables as in the $E_0:pH$ curves, the uniformity of the percentage reduction:E_h curves makes it easy to estimate the potential at any percentage reduction from the chart and the data of table 3.

Since it is difficult to distinguish between the lower degrees of reduction an indicator is chiefly useful at 70 to 95 per cent reduction.

Let it be found for instance that indigo tetrasulphonate in a solution of pH 6.0 is 80 per cent reduced. The chart shows that

50 per cent reduction corresponds to $E_h = 0.007$. Hence at 80 per cent reduction $E_h = -0.011$.

Among the systems shown in figure 9 several must be rejected from practical use. Thus indicators such as Lauth's violet and indigo monosulphonate must be rejected because of their low solubilities. The same would apply to the methylene blue system because of the very low solubility of methylene white at neutral reaction were it not for the fact that the intense tinctorial power of the dye permits its use in extreme dilutions. Among the indophenols are many which have such low dissociation constants that the extraordinary blue of the dissociated compound does not appear in neutral solutions. However, by introduction of halogen substituents the dissociation constant can be increased until in 2, 6-dichlorophenol indophenol pK_a is 5.7. This compound gives brilliantly blue neutral solutions.

No indicators suitable for potentials more positive than those of the m-bromophenol indophenol system (9 of fig. 9) are yet available, and it may be that the chemist will look in vain to the biochemist for efforts to fill the gap between this and the region of oxygen over-voltage. The reason is that every living cell so far tested reduces these indophenols almost instantaneously. Consequently only the incentive of special problems yet to be defined will encourage the biochemist to search for more positive indicator systems.

In the extreme negative zone figure 9 shows a large gap and this gap is of particular interest to the bacteriologist because it is attained in cultures of many bacteria. A portion of this gap will doubtless be covered by compounds now under investigation at this laboratory.

It is of course obvious that the charting of indicator characteristics is the beginning of indicator theory as applied to titrations. It is also obvious that the possession of such definite values as are shown in figure 9 enables one to tell rapidly the approximate oxidation-reduction intensity of any system which can enter into simultaneous equilibrium with one of the listed indicators.

Later I shall touch briefly upon certain biochemical applications

of these indicators but shall refer the reader to forthcoming papers for details.

In the meantime let the reader remember that hundreds of applications of methylene blue-reduction have been made without the quantitative interpretations now available.

THE EFFECTS OF SUBSTITUTION

If we consider a case to which equation (8) applies and for which the numerical values of K_1 and K_2 fall within the experimental range of $[H^+]$ there can be established not only the "normal potential," E_o, but the values of K_1 and K_2. An acidic or basic group common to oxidant or reductant will not be apparent unless the dissociation constant of such a group *changes* when the substance is oxidized or reduced. Then, if the change is of sufficient magnitude, both K-values are determinable as already illustrated in a previous section (see page 143). Thus it is often possible to establish several characteristic constants for a given system.

If then a substitution in the molecule is made, the influence of this substitution upon the values of several constants can be established. Thus we have a beautiful and exact set of data on substitution.

However, there often remain difficulties of interpretation. Conant, Kahn, Fieser and Kurtz (1922) in discussing a case where equation (8) was applied remark: "There is nothing to indicate that the two constants . . . . are the real dissociation constants of the reduced form except that the equation can be developed on this basis." Their meaning is not very clear, for it can be shown that if the same basis of reference could be reached in handling different methods (colorimetric, potentiometric, conductimetric, etc.) the constants would be the same whatever the method of approach. On the other hand, there is nothing in the method under discussion which helps us in the allocation of the constants. For this we must depend upon structural chemistry. It is just here that structural chemistry presents a most serious difficulty. In a reductant such as (I)

is the first hydrogen to dissociate that adjacent to the bromines or that of the other phenolic group, and does the replacement of bromine by methyl alter whatever may be the order of dissociation in (I)? In the oxidant is the predominant structure (II) or (III) and if (II) does it become wholly or partially of type (III) or remain type (II) on replacing bromine by methyl?
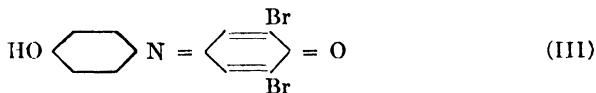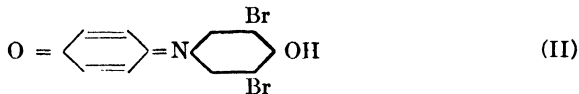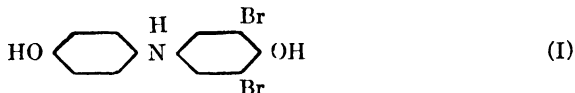
Certain hints may be obtained such as those noted in the case at hand by Cohen, Gibbs and Clark (1924) but perfectly definite evidence is lacking.

However, some problems are in a fair way to definite settlement. For instance Heller (1912) claimed that two different indophenols result from the condensation in the one case of p-amino phenol with m-cresol and in the second case from the condensation of (p-amino-m-cresol) 6-amino-3-hydroxy-1-methyl benzene with phenol. Cohen, Gibbs and Clark (1924) proceeding with different chloroimides which should have given Heller's isomers obtained compounds which acted the same within the limits of error of potentiometric measurements; as might well have been expected if we regard Heller's isomers as tautomers. More positive evidence could be obtained with substituents of greater effect than that of methyl.

The methods under discussion will not reveal the presence of tautomers in mobile equilibrium but they will definitely reveal stable isomers when such isomers have different characteristic

constants.   Consequently Conant and Fieser (1924) were able
to show for hydroxy-naphthoquinone
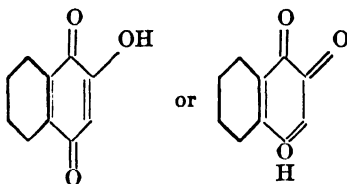
that either only one isomer was present or else that the two forms
are tautomers in mobile equilibrium.

These instances may suffice to suggest on the one hand a
number of cases where potentiometric measurements can aid in
the solution of problems of structural chemistry, and on the
other hand the kind of problem still to be solved by structural
chemistry before the allocation of substitution effects of the kind
we are discussing can become definite.

The space available does not allow an adequately detailed
review of the numerical values now available on substitution
effects.   Moreover a quantitative formulation of the data must
await either sufficient material for statistical analysis or else a
key constructed without *ad hoc* assumptions.

Nevertheless, it is interesting to note that among the limited
types of compound investigated by Biilmann, LaMer and Baker,
Conant and his coworkers and the investigators at the Hygienic
Laboratory, halogens increase and alkyls decrease potentials;
sulphonic acid groups and carboxyl increase and hydroxyl,
methoxy, and phenyl decrease potentials.

In figure 2 (page 139) there have already been shown the effects
of one series of substitution.   Figure 10, taken from the disserta-
tion of Baker, shows graphically the general relations among a
series of substituted quinones accurately studied by LaMer and
Baker (1922).   In each of tables 4, 5 and 6 are some comparable
data, which are given only as samples of much more extensive
data to be found with interesting comments in the original papers
by Conant and his coworkers and by the investigators at this
laboratory.
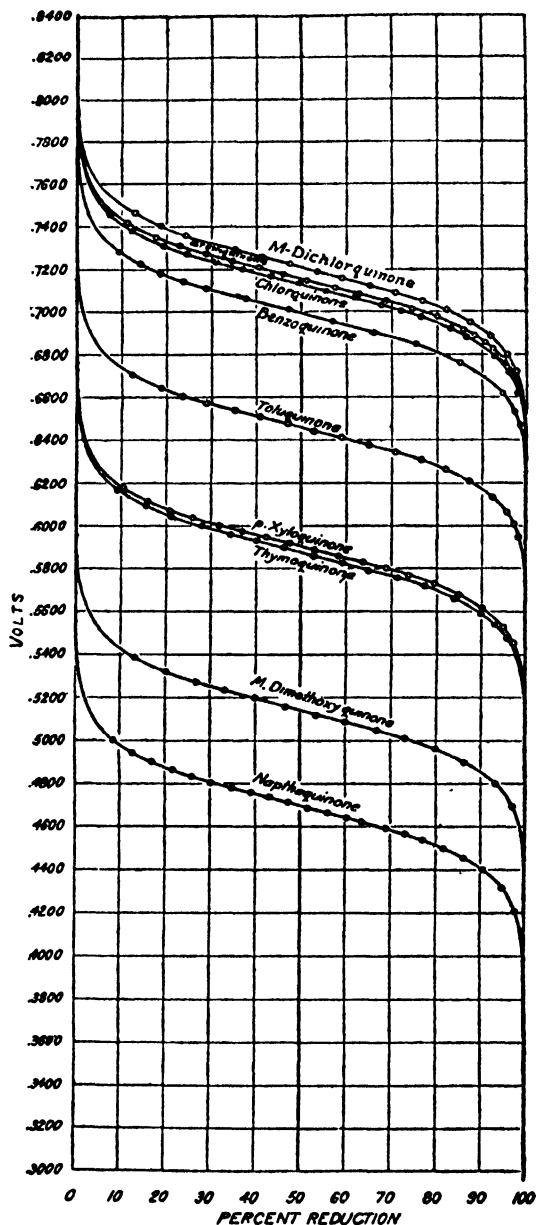
FIG. 10. RELATION OF ELECTRODE POTENTIAL TO PERCENTAGE REDUCTION SHOW-
ING EFFECTS OF SUBSTITUTION

After Baker

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Conant and Fieser (1923) finding that some of the systems they wished to compare were not adapted to measurements in aqueous solutions used the principle outlined in a previous section in their

TABLE 4

Compiled from Conant's data

E.M.F. of cell: H_2 (1 atmos.) Pt	0.5 M HCl in 95 per cent ethanol at 25°	0.5 M HCl + S_o = S_r in 95 per cent ethanol	Pt$^+$
S_o/S_r SYSTEM NAMED BY OXIDANT		E.M.F.	
1,2 naphthoquinone...		0.580	
1,4 naphthoquinone...		0.495	
2 chloro-1,4 naphthoquinone................................		0.510	
2,3 dichloro-1,4 naphthoquinone............................		0.499	
2 bromo-1,4 naphthoquinone.................................		0.508	
1,4 napthoquinone-2-sulfonic acid...........................		0.553	
2 hydroxy-3 chloro-1,4 naphthoquinone......................		0.349	
2,3-diphenoxy-1,4 naphthoquinone...........................		0.456	
1,2 anthraquinone..		0.492	
9,10 anthraquinone...		0.156	
2 methyl-9,10 anthraquinone................................		0.152	
1 chloro-9,10 anthraquinone................................		0.175	
2 chloro-9,10 anthraquinone................................		0.202	
9, 10 anthraquinone-2-carboxylic acid.......................		0.213	
methyl-9,10-anthraquinone-2-carboxylate....................		0.224	
ethyl-9,10 anthraquinone-2- carboxylate....................		0.223	

TABLE 5

Normal potentials, E_o, and dissociation constants of groups formed by reduction.   25°
(after Conant, Kahn, Fieser and Kurtz, 1922)

SYSTEM NAMED BY OXIDANT	E_o	K_1	K_2
9,10 anthraquinone 1 sulfonic acid..........	0.195	4×10^{-9}	
9,10 anthraquinone 1,5 disulfonic acid......	0.239	3×10^{-11}	
9,10 anthraquinone 1,8 disulfonic acid......	0.206	7×10^{-9}	
9,10 anthraquinone 2 sulfonic acid..........	0.187	1×10^{-8}	5×10^{-11}
9,10 anthraquinone 2,6 disulfonic acid......	0.228	8×10^{-9}	3×10^{-11}
9,10 anthraquinone 2,7 disulfonic acid......	0.229	2×10^{-8}	3×10^{-11}

study of aqueous and alcoholic solutions. They were able to show that parallel data of value can be obtained by measurements in aqueous and alcoholic solution. This was an important advance in that it broadened the available material and led to a

later illuminating study (Conant and Fieser, 1924) of some 35 additional systems.

Although the limitations of the method and the inherent errors leave something to be desired, the most accurate applications of the method to the determination of acidic and basic dissociation constants are those of the Hygienic Laboratory workers. These authors have shown how necessary is a fair accuracy in the estimation of such constants if there is to be avoided the confusion due to unrecognized crossings of E'_o: pH curves.

TABLE 6

Effects of substitution on E_o and pK values of indophenols

Type compound called phenol indophenol: $O = \langle \begin{smallmatrix} 2 & 3 \\ 1 & 4 \\ 6 & 5 \end{smallmatrix} \rangle = N \langle \begin{smallmatrix} 2' & 3' \\ 1' & 4' \\ 6' & 5' \end{smallmatrix} \rangle OH$

SYSTEM NAMED BY OXIDANT*	E_o	pK_o	pK_r	pK_i
Phenol indophenol..................................	0.649	8.1	9.4	10.6
2-methyl-phenol indophenol........................	0.616	8.4	9.5	10.9
3-methyl-phenol indophenol........................	0.632	8.6	9.6	10.7
2 isopropyl-5 methyl-phenol indophenol.............	0.592	8.8	9.9	10.8
2 methyl-5 isopropyl-phenol indophenol.............	0.593	8.9	9.9	10.7
2-bromo-phenol indophenol.........................	0.659	7.1	8.5	10.2
3-bromo-phenol indophenol.........................	0.670	7.8	9.0	10.3
2-chloro-phenol indophenol........................	0.663	7.0	8.4	10.3
3'-5' dichloro-phenol indophenol...................	0.668	5.7	7.0	10.1
3'-5'dibromo-phenol indophenol....................	0.668	5.7	7.0	10.1
2 chloro-3', 5'-dichloro-phenol indophenol..........	0.668	5.8	7.1	8.8
2 methyl-3',5'-dichloro-phenol indophenol..........	0.639	5.5	7.1	10.4

* For discussion of tautomerism, see page 162.

Indeed there is involved a very interesting question which will arise when attempts are made to compare systems of different type. What is to be the standard state for comparison? While certain hydroquinones can be brought to the fully dissociated state other reductants cannot. On the other hand certain compounds such as methylene blue cannot be brought to the undissociated state.

It seems to me that there is more than a mere question of convention involved and I may suggest what I have in mind by an interesting fact.

Among the quinones halogen substitution increases the *normal*

potential much less than alkyl substitution decreases, taking benzoquinone as a standard of comparison. The same tendency in less marked degree is observed among simple indophenols. On the other hand among the indophenols the effect of halogen substitution upon K_o-*dissociation constants* tends to be greater than the effect of alkyl substitution.

Thus one set of data, for instance "normal potentials" may not give as full an expression of the effects of substitution as can readily be obtained.

Now undoubtedly what we are providing in these data is some sort of comparative measurement of the electron constraints within the molecule. Cohen, Gibbs and Clark (1924) have therefore suggested that possibly the most illuminating comparisons of potentials would be found among completely ionized systems could a series of these be obtained. Conant and his coworkers give some good reasons for choosing the undissociated state of hydroquinones as the standard state.

The real difficulty is not in finding a *convenient* state for the comparison of one group of compounds but in the element of relativity which permeates the whole subject. Of this the interpreter of the substitution data must take full account.

In the meantime the basic facts of the quantitative effects of substitution are being found to have very considerable value in a number of directions. It is hoped that they will soon receive an illuminating interpretation.

TYPES OF COMPOUND SUCCESSFULLY STUDIED

It is important for the advancement of the subject to know its limitations as suggested in the types of compound which have yielded good or fairly reliable potentiometric data.

Foremost in the number of cases examined are quinone-quinol systems of which benzoquinone-benzohydroquinone
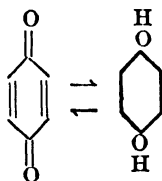
is the prototype.   Including in this group the naphthoquinones and anthraquinones we find data on about 50 systems in the papers of Biilmann (1920) LaMer and Baker (1922) and Conant and his coworkers (1922–24), the latter group of workers having contributed the greater number of data.

The corresponding diamines are being studied in this laboratory.

The indophenols of which the simplest member is

$$O = \left\langle \overline{\overline{}} \right\rangle = N \left\langle \right\rangle OH$$
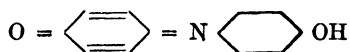
may be considered as oxidants of substituted amino phenols. Clark and Cohen (1923), Cohen, Gibbs and Clark (1924) and Gibbs, Cohen and Cannan (1925) have successfully measured some 26 of these systems.   In addition they have unpublished data for certain indamines.

The change

$$\begin{array}{c} \rightleftharpoons \end{array}$$
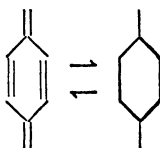
evident in the above cases is still evident in the transformation methylene white $\rightleftharpoons$ methylene blue and in the corresponding system of Lauth's violet.   Clark, Cohen and Gibbs (1925) have measured these systems.

In the quinones there is the conjugated system

$$O = C - C = C - C = O$$
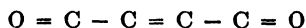
which may be found in the following disputed formula of indigo
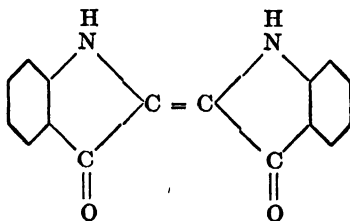
The indigo sulphonates have been reported upon by Sullivan, Cohen and Clark (1923) and Conant and Lutz (1924) have reported preliminary data on two sulphur indigoes and alizarin indigo.

Adopting Biilmann's formulae we have Biilmann and Lund's (1924) data on the dialuric acid-alloxan system

$$
\begin{array}{ccc}
\text{HN—C=O} & & \text{HN—C=O} \\
\mid \quad \mid \text{H} & & \mid \quad \mid \text{OH} \\
\text{O=C} \quad \text{C} & \rightleftharpoons & \text{O=C} \quad \text{C} \\
\mid \quad \mid \text{OH} & & \mid \quad \mid \text{OH} \\
\text{HN—C=O} & & \text{H—N—C=O}
\end{array}
$$
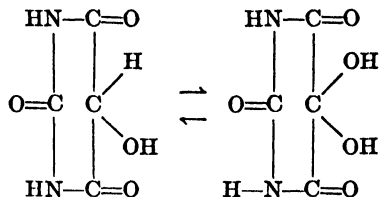
and a methylated pair of derivatives.

By allowing for potential drifts which could easily be ascribed to a semidine or benzidine rearrangement of their hydrazo compounds Biilmann and Blom (1924) have found reasonable data for two azo-hydrazo systems.

Conant and Lutz (1923) describe nitroso benzene and nitroso-β-naphthol as yielding reliable potentials in their reversible reductions to phenylhydroxyl amine and 1-hydroxylamino-2-naphthol respectively.

In addition there is the highly important study by Conant (1923) on hemoglobin. The equilibrium between this blood pigment and oxygenated hemoglobin seems not to be susceptible to potentiometric measurement. On the other hand Conant finds that the hemoglobin-methemoglobin system can be followed potentiometrically. While the experimental data leave much to be desired in accuracy the equation

$$
E_h = E_o - \frac{RT}{F} \, ln \, \frac{\text{Hemoglobin}}{\text{Methemoglobin}}
$$

is fairly well satisfied at constant pH. There is a change of E_o' with change of pH such as might be expected from a change in the dissociation constants of one or more groups common to oxidant and reductant. The one-equivalent concerned in the reduction of methemoglobin to hemoglobin is in marked contrast

to the two equivalents which Conant's preliminary data indicate are concerned in the reduction of hematin to hemochromogen. These considerations suggest that the hemoglobin-methemoglobin system involves the one equivalent necessary in a ferrous-ferric transformation.

Although somewhat out of place in our scheme of presentation the later papers by Conant and Fieser (1925) on methemoglobin which have just come to hand may be mentioned here. In the first paper the simultaneous equilibrium between the hemoglobin-methemoglobin system, the hemoglobin-oxyhemoglobin system and the ferro-ferricyanid system have been studied in more detail, confirming the main conclusions of the earlier paper and giving additional data of value to the analysis of oxyhemoglobin solutions. In the second paper the new data are shown to lead to a simple method for the determination of methemoglobin in the presence of its cleavage products.

Whether Dixon and Quastel's (1923) study of cysteine can properly be included is questionable. Were I reviewing the entire subject I should like to discuss this highly interesting case but shall now arbitrarily classify it as belonging outside the realm which I am reviewing.

SIDE-LIGHTS ON MECHANISM

It should of course be perfectly well recognized that potentiometric measurements reveal nothing definite regarding mechanisms of oxidation-reduction and that equations which imply any mechanism are purely formal.

At the same time certain *comparative* data furnished by the potentiometric measurements provide material for *intuitive* deductions.

The more accurate data on reduction of substances having a quinoid structure have left not the slightest doubt that the two equivalents concerned are in some way *paired* in their energetics. There is no trace of stepwise reduction corresponding *structurally* (as Conant has pointed out to me in conversation) to an intermediate between a quinoid and a quinol, or analogous to the stepwise dissociation of acids and bases. From the point of

view of the *electronic configurations* of the molecule this corre-
sponds to no stable intermediate between the configuration of
quinone and that of quinol with its *two additional electrons*.

On the other hand the hydrogens which might be regarded as
the more directly concerned equivalents involved in the trans-
formation have been shown, in a variety of indigoes, indophenols
and thiazines, to have very greatly different ionization constants
and hence very different free energies of ionization. Further-
more the indophenol systems lie in a region of potential which by
the application of theoretical relations for the oxy-hydrogen gas
cell can be shown to indicate physically insignificant partial
pressures of hydrogen in equilibrium with the systems. The
implication which has been discussed by Cohen, Gibbs and Clark
(1924) is that the reduction in these cases consists essentially in
the transfer of an *electron pair* accompanied or not accompanied
by hydrogen ions according to the state of acid-base equilibrium
in the solution. This is the kind of implication which cannot
definitely disprove Wieland's very hypothetical mechanism of
biological oxidation by hydrogen-transport which is now quite
in vogue and which he supports by citing the conduct of reducible
dyes, but it doubtless would have directed speculation into other
channels had it been appreciated earlier.

The types of compounds which have furnished reliable potentio-
metric data are comparatively few. To generalize upon this is
very dangerous but it is interesting to guess the significance.

In most if not all of the cases for which we have reliable data
there is at least one hydrogen associated with the change of
oxidant to reductant which ionizes within the experimental
range of pH leaving at least one unguarded charge upon
practically all the molecules at high pH and upon a few at other
regions of pH.

Secondly there is frequently a nucleus such as we picture in
the quinone-quinol rings, or in the electron shells of nitrogen and
of iron where the gain or loss of electrons unaccompanied by
neutralizing ions is possible without complete loss of the system's
stability.

Accordingly the criterions of a reversible system capable of

potentiometric measurement with the aid of electrodes should be first a system in which ionization uncovers at least one vulnerable point and second a system containing what may be called a reservoir effect, i.e., an electronic configuration not instantly made unstable by loss or gain of electrons and therefore capable by itself of taking up or releasing electrons as they flow to and from an electrode in the course of potentiometric balancing.

It has long since been found impossible to treat the *actual* conduct of the electrode under the conditions now being discussed as if it were that of a hydrogen electrode, although this, as a formalistic treatment, is sometimes convenient.

These guesses lead directly to the consideration of those systems which have no very definite effect upon the electrode and to the so-called irreversible oxidation-reductions. No review such as this would be at all adequate if it failed to mention this vast subject. Here let me remind the reader that in the introduction to this review I promised to mention what is perhaps the most important of all the reasons which may be advanced for the scarcity of potentiometric data on organic systems. It is simply that the systems regarded as most important by the organic chemist and the physiologist have resisted the methods of approach we have been discussing.

Recent adventures in this important realm will be discussed by Dr. Conant and I shall try not to trespass upon the review he has promised. But I know he will not object if in my final remarks I touch very briefly upon certain studies of a peculiar kind of so-called irreversible system in which I have been particularly interested.

BIOLOGICAL STUDIES AND CONCLUDING REMARKS

The processes of oxidation-reduction which are peculiar to the chemistry of the living cell have received a vast amount of attention. The greater part of this has been centered upon the mechanisms by which molecular oxygen enters into the chemistry of life. I would emphasize the difficulty incident to the study of a set of oxidative processes continuously being opposed by that powerful trend toward higher and higher reductive inten-

sities which is uncovered whenever the cell is isolated from extraneous oxidants. Upon the cause of this trend it would be idle to speculate but the trend is far more generally characteristic of the living cell than respiration without which many organisms do very well (cf. review by Clark, 1924).

In the study of the reductive trend will the electrode be of service? Gillespie's (1920) work suggests that it will. After extensive experiments which confirmed the main features of Gillespie's observations on bacterial cultures, I concluded that an answer worthy of the importance of the question could be found only after a better understanding of simple and reversible systems. This was the origin of potentiometric studies on oxidation-reduction indicators (Clark, 1919–1920).

I believe there should now be no doubt that the establishment of equilibrium constants makes it possible to reinterpret quantitatively in terms of potential the intensities of reduction revealed by the decoloration of indicators such as methylene blue which have been very extensively used in a purely qualitative way to build elaborate theories. Now it is of course obvious that, having shown a mixture of methylene blue and methylene white to affect an electrode in a perfectly definite way, we cannot gain much that is new by using an electrode in a suspension of cells containing partially reduced methylene blue. On the other hand we have shown that with the electrode *in the absence* of any indicator it is possible to follow in much greater detail the course of reduction in the Schardinger reaction, in the reduction test of milk, in the putrescibility test of sewage. The diagnostic differential reduction by different species of bacteria is recorded by potentiometric measurements quite as well and perhaps better than by indicators. Phenomena of washed and unwashed cell-suspensions in the presence and absence of metabolites, which have hitherto been studied chiefly with the aid of methylene blue, can be followed in greater detail by potentiometric measurements.

In short the cumulative results, reproducing as they do in terms of electrode potential-difference all the chief features of dye reduction, may be considered as evidence that the cautiously

interpreted potentiometric measurements have at least as much significance as dye-reduction.

However we must proceed with caution. We encounter in these cell-suspensions no equilibrium having a mobility comparable to that of an ordinary acid-base system. Consequently poising[2] action is either obscured by slow rates of adjustment or is absent and the activity of the uncontrolled partially cytolysed cells induces a continuous change in electrode potential. Thus the type of problem to be considered is very different from that of the acid-base equilibria in living tissue. A drifting potential may be due to so many causes that unless we can give a reasonable interpretation, as Bülmann and Blom have done for their azo-hydrazo systems, we would ordinarily reject our data. But in the case at hand the importance demands persistent investigation of the facts.

Among the many interesting facts are the following. We never find E_h potentials more positive than about $+0.2$ at pH 7 as measured *both* by indicators and electrode even after air has been bubbled through the cell-suspension! Cultures of certain anaerobic bacteria, as measured by electrodes and independently by such indicators as are available for rough estimates, can not only induce the potential of the hydrogen electrode but also a definite although slight overvoltage! Within the intermediate range of potential, cell-suspensions act as if there were present at any moment sufficient active material to prevent serious polarization in the balancing of potentials and yet insufficient to prevent serious change of potential when *active* oxidants or reductants are added. A more adequate discussion will appear in a forthcoming paper from this laboratory.

In short the compounds present in these cell-suspensions seem to be activated sufficiently to affect indicators and electrodes in a comparable way which is certainly suggestive but short of satisfactory. This casts the problem back again to the study of more definite and more simple systems which we still have to understand better. That this would become the main problem was

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[2] Clark, 1923, suggests the term "poising action" as the oxidation-reduction analogue to acid-base buffer action.

apparent to me at the beginning of my biochemical studies in 1919 but at that time relations were quite obscure which have now become plain by the study of the reversible systems discussed in this review.   I have no doubt that while definite limitations of the methods will be found it will be realized that there is no sharp line of demarkation between systems amenable to these methods and systems which are not.   The problem is to find how far the methods will be of use.   But here I am encroaching upon a field beyond the scope of this review.

In closing I may indicate the significance of the recent studies on reversible systems by suggesting that the organic chemist with the infinite variety of structure at his disposal may soon discover why it is that so many inorganic systems have resisted potentiometric measurement.   If the full force of this suggestion be appreciated it will be realized that the significance transcends the importance of the immediate problem cited.

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THE CONFIGURATIONAL RELATIONSHIPS OF THE SUGARS, HYDROXY ACIDS, AMINO ACIDS AND HALOGEN ACIDS

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In recent years, chemists have devoted much attention to the configurational relationships of monosaccharides, α-amino, α-hydroxy and α-halogen acids.

The field of chemistry in which the achievements of stereochemistry have been the greatest is undoubtedly that which deals with the configurational relationships of monosaccharides. The name of Fischer is preeminent among all workers in this field, but the name of Kiliani should also be remembered in this connection as he was the one to furnish a method for the synthesis of a higher monosaccharide from a lower one and Fischer made much use of this method.

The relationships of simple carbohydrates is a matter of common knowledge and need not be reviewed here. The most rational and clearest presentation of these relationships is found in the article of Rosanoff. A comprehensive summary on simple sugars in general is to be found in the monograph of Armstrong.

Fischer, in his day the greatest master of stereochemistry and also the greatest authority on sugar chemistry, was the first to point out the possibility of correlating the configuration of hydroxy acids with the configuration of monosaccharides. The pioneer work in this direction was done by Fischer himself and further progress was made by workers who received their training aṅd inspiration from him. Fischer also realized the importance of correlating the configurations of amino acids with those of hydroxy acids and made some efforts towards that end but soon

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realized that the usual chemical methods were inadequate for that purpose. This problem received considerable attention in other laboratories and substantial progress towards its solution has been made in recent years. This review will be devoted principally to these achievements. A brief review, however, will be given of the work on the correlation of the configurations of hydroxy acids with those of the sugars and of the mutual relationships of the configuration of individual amino acids.

The work on the two last-mentioned problems was accomplished by purely chemical methods. The chemical reactions employed were such that did not involve the asymmetric carbon atom.

CORRELATION OF HYDROXY ACIDS WITH SUGARS

The first effort of a comprehensive treatment of this subject is that by Fischer. Prior to Fischer, isolated attempts were made in this direction. The first important contribution by Fischer was the one which established the configuration of d-tartaric acid, which was prepared by the degradation of l-rhamnose through the following steps:

dextro-tartaric acid.

III
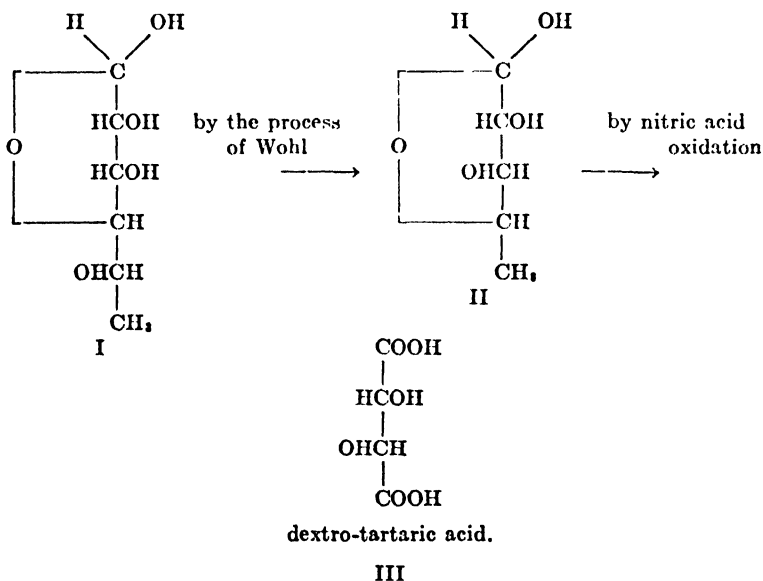
In 1875 Bremner converted by the action of hydroiodic acid dextro-tartaric into dextro-malic acid and in this he saw conclusive evidence of the similarity of the allocation of the hydroxyl in dextro-malic and dextro-tartaric acids.

Prior to the time of Fischer's work, it had been shown that dextro-malic acid could be obtained from levo-aspartic acid. Fischer, in the early days of his work, thought that these three independent observations justified the conclusion that dextro-tartaric, dextro-malic and levo-aspartic acids are configurationally related.

But in 1893, the phenomenon of Walden Inversion was discovered and thereupon Fischer, in 1896, qualified the conclusions regarding the configuration of the four substances by a proviso that a Walden Inversion had not taken place in the course of the reactions which led from one to the other. As it happened, subsequent and more reliable methods which excluded the possibility of Walden Inversion established the same relationships which were formulated by Bremner.

The following figures, IV, V, VI, VII, VIII illustrate the set of reactions by which dextro-tartaric acid was converted into dextro-malic acid by K. Freudenberg and F. Braun.

$$
\begin{array}{ccccc}
\text{COOH} & \text{COOCH}_3 & \text{COOCH}_3 & \text{COOH} & \text{COOH} \\
| & | & | & | & | \\
\text{HCOH} & \text{HCOCOCH}_3 & \text{HCOCOCH}_3 & \text{HCOH} & \text{HCOH} \\
| \;\rightarrow & | \;\rightarrow & | \;\rightarrow & | \;\rightarrow & | \\
\text{OHCH} & \text{OHCH} & \text{CHCl} & \text{CHCl} & \text{CH}_2 \\
| & | & | & | & | \\
\text{COOH} & \text{COOCH}_3 & \text{COOCH}_3 & \text{COOH} & \text{COOH} \\
\text{dextro} & & & & \text{dextro} \\
\text{IV} & \text{V} & \text{VI} & \text{VII} & \text{VIII}
\end{array}
$$
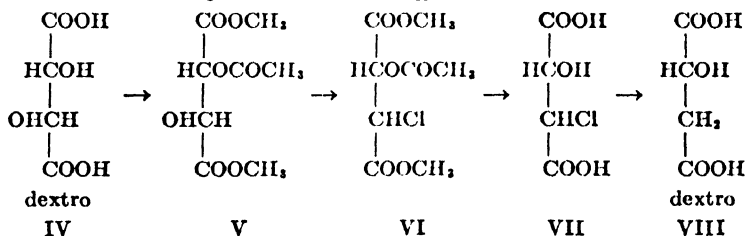
In an investigation which preceded the one just mentioned, K. Freudenberg correlated the configurations of malic, glyceric and lactic acids by the following set of reactions.

$$
\begin{array}{ccccc}
\text{COOH} & \text{CONH}_2 & \text{COOH} & \text{COOH} & \text{COOH} \\
| & | & | & | & | \\
\text{OHCH} & \text{OHCH} & \text{OHCH} & \text{OHCH} & \text{OHCH} \\
| \;\rightarrow & | \;\rightarrow & | \;\rightarrow & | \;\rightarrow & | \;\rightarrow \\
\text{CH}_2 & \text{CH}_2 & \text{CH}_2 & \text{CH}_2\text{NH}_2 & \text{CH}_2\text{OH} \\
| & | & | & & \\
\text{COOH} & \text{CONH}_2 & \text{CONH}_2 & & \\
\text{natural,} & \text{malamid} & \text{malaminic} & \text{levo} & \text{dextro-glyceric} \\
\text{levo} & & \text{acid} & \text{iso-serine} & \text{acid.} \\
\text{IX} & \text{X} & \text{XI} & \text{XII} & \text{XIII}
\end{array}
$$

COOH   COOH
| |
OHCH → OHCH
| |
CH_2Br CH_3

dextro-3-   dextro-
bromo   lactic
lactic acid.   acid.

XIV   XV
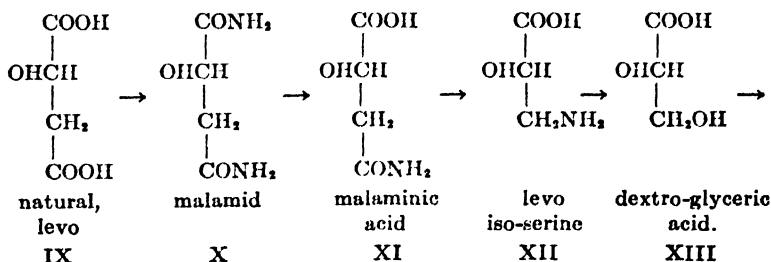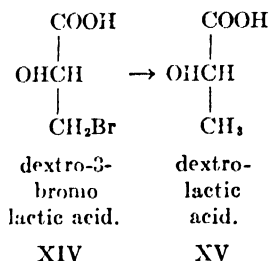
In a very ingenious and laborious way, Wohl and his co-workers correlated on the one hand, the configuration of glyceric aldehyde with tartaric acid and on the other, that of glyceric aldehyde with glyceric acid. Thus, in coöperation with Momber, he established the relationship between dextro-glyceric aldehyde and levo-tartaric acid in the following way:

CHO   COOH
| by addition |
HC—OH   of prussic   OHCH
| acid ————→ |
CH_2OH HCOH
                        |
                        CH_2OH

dextro-   levo-
glyceric   tartaric
aldehyde   acid.

XVI   XVII
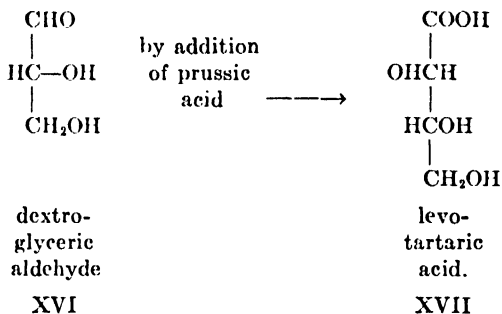
With R. Schellenberg he oxidized glyceric aldehyde to the corresponding acid,

CHO   COOH
| |
HCOH ————→   HCOH
| |
CH_2OH CH_2OH

dextro-   levo-
glyceric   glyceric
aldehyde,   acid.

XVIII
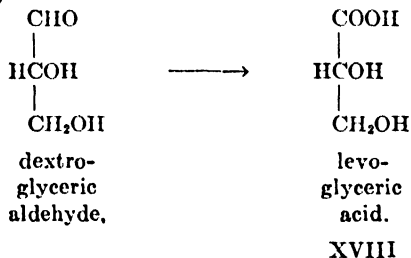
Thus, on the basis of all this very ingenious and technically difficult work the following relationships are established. Carbon atoms 3 and 4 of glucose are taken as points of reference.

```
CHO
 |
CHOH            COOH
 |               |
OHCH            OHCH              CHO
 |               |                 |
HCOH    ⟶      HCOH  (as carbon 4  HCOH   (as carbon 4  ⟶
 |               |     of d-glucose) |      of d-glucose)
HCOH            COOH              CH₂OH
 |
CH₂OH

d-glucose.      levo-tartaric acid.      dextro-glyceric
                                              aldehyde.


COOH                    COOH                    COOH
 |                       |                       |
HCOH  (as carbon 4      HCOH  (carbon 4         HCOH
 |      of d-glucose) ⟶  |      of d-glucose) ⟶  |
CH₂OH                   CH₂                     CH₃
                         |
                        COOH

levo-glyceric acid.     dextro-malic acid.     levo-lactic
                                                   acid.
```
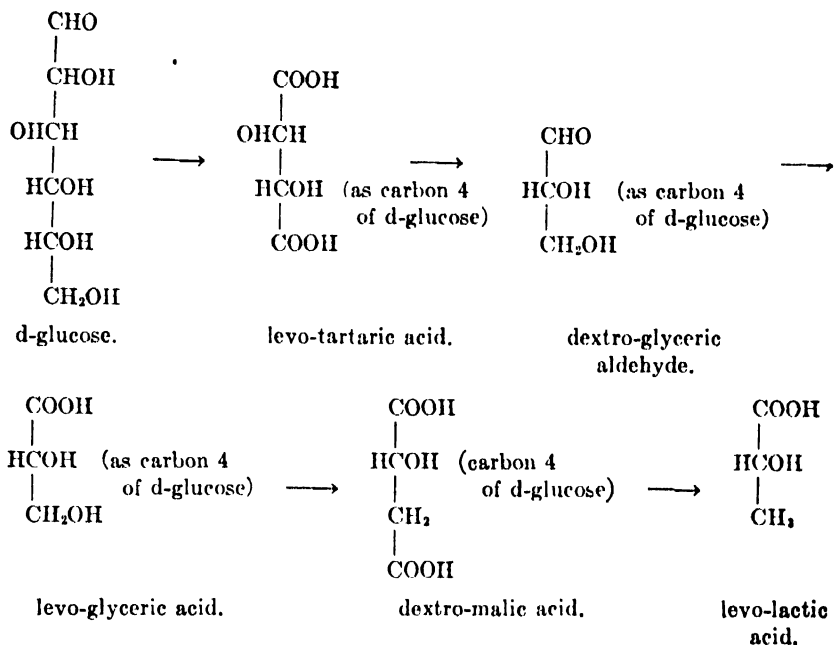
XIX

The dextro and levo, refer only to the direction of rotation whereas the letter *d*, as in *d-glucose*, indicates that the sugar belongs to the d series. Rosanoff's classification of the d and l series should be generally accepted. On the basis of this classification, dextro-tartaric, dextro-malic, levo-glyceric and levo-lactic belong to the d series. The designation of d and l series is a matter of convention; the relationship given in figure XIX are facts and correlate the other substances with d-glucose, if carbon atom (2) of d-glucose is taken as point of reference.

STEREOCHEMICAL RELATIONSHIPS OF 2-AMINO ACIDS

The pioneer work in this direction was also done by E. Fischer. In coöperation with K. Raske, he converted levo-serine into levo-1-amino-2-chloropropionic acid and this into dextro-alanine and later, also in coöperation with Raske, he converted levo-1-

amino-2-chloropropionic acid into levo-cystine.   The reactions involved are presented in the following figures:

                                                    COOH
                                                     |
                                                   NH₂CH
                                                     |
                                                    CH₃

    COOH   COOH   dextro-alanine.
     | |
   NH₂CH   ⟶   NH₂CH
     | | COOH
   CH₂OH   CH₂Cl |
                                                     NH₂CH
                                                       |
                                                     CH₂SH

   levo-serine   levo-1-amino-2-   levo-cystine.
                    chloro-propionic
                    acid

$$\begin{array}{ccc}
\text{COOH} & \text{COOH} & \\
| & | & \\
\text{NH}_2\text{CH} & \text{NH}_2\text{CH} & \\
| & | & \\
\text{CH}_2\text{OH} & \text{CH}_2\text{Cl} &
\end{array}$$
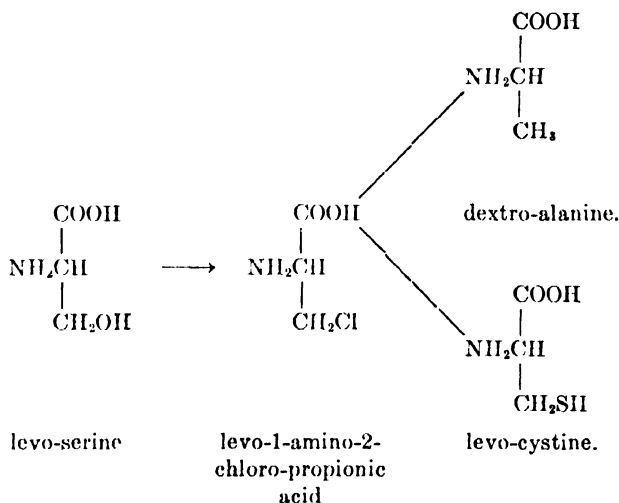
It is evident that all these amino acids belong to one and the same series although they rotate in opposite directions.   More recently, Karrer in coöperation with Schlosser converted levo-asparagine into dextro-diamino-propionic acid through the following set of reactions.

    CONH₂   CH₂NH   CH₂NH₂
     | | ＼CO |
    CH₂   ⟶ | ／   ⟶   CHNH₂
     | CHNH |
   CHNHCOCH₃ | COOH
     | COOH
    COOH

   levo-asparagine.   levo-glyoxalidon   dextro-diamino
                       2-carbonic acid-5.   propionic acid.

       XXI   XXII   XXIII
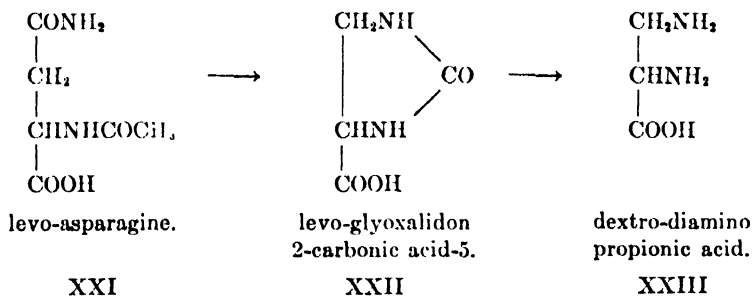
    Later, Karrer converted dextro-serine into levo-diamino-propionic acid, thus having correlated levo-aspartic acid with levo-serine.

```
        COOH                    COOH
         |                       |
      NH₂CH        ⟶          NH₂CH
         |                       |
      CH₂OH                   CH₂NH₂
    levo-serine            dextro-diamino
                              propionic
```
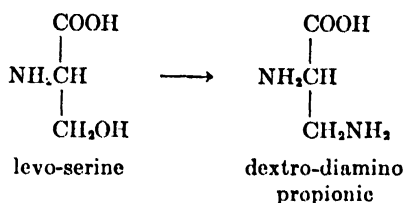
<div align="center">XXIV</div>

Mention also should be made of the work of E. Waser and E. Brauchli, who advanced evidence in favor of configurational relationship between l-tyrosine and l-phenylalanine.

The latest contribution to the correlation of amino acids is the work of W. Langewhick from the laboratory of K. Freudenberg. This author converted histidine into benzoyl-levo-aspartic acid by the following set of reactions.

```
COOCH₃            COOCH₃                COOCH₃                    COOH
  |                 |                     |                        |
CHNH₂             NHCOC₆H₅CH           NHCOC₆H₅CH  C₆H₅COHN CH      CH
  |       ⟶        |         ⟶          |            ⟶           |
CH₂               CH₂        through    CH₂                      CH₂
  |                 |        ozone.      |                        |
C  NH             CNHCOC₆H₅            CONHCOC₆H₅                COOH
 ‖    \             ‖
 ‖     CH          CH · NHCOC₆H₅
 ‖    //
 C—N
   Hystidine                                          benzoyl-levo-
 methyl ester                                         aspartic acid.
```
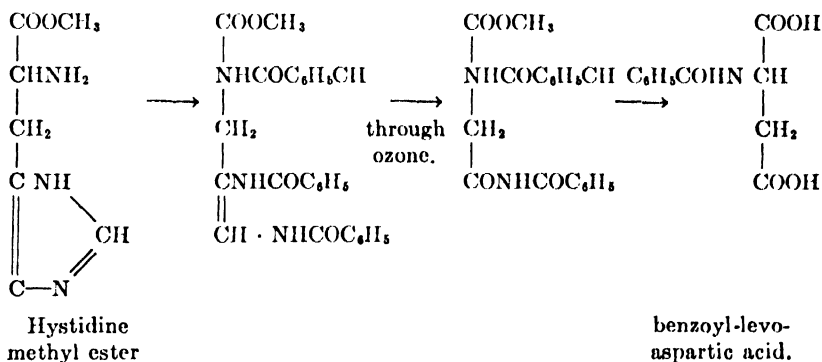
<div align="center">XXV</div>

This concludes the list of amino acids of which the mutual stereochemical relationships have been established by chemical reactions which did not involve the asymmetric carbon atom.

While the work thus far reviewed was in progress, new problems came to the fore of which the solution at that time and still now seems unapproachable by the purely chemical method. Prominent among these were: The differentiation between dynamic isomers such as α- and β-sugars, ring isomers in the sugars, and above all, the problems which arise from the phenomenon of Walden Inversion.

For the solution of these new problems, recourse was taken to physical methods and the review which is to follow will be devoted to a survey of efforts in this direction. Several authors were engaged on these problems. The methods employed in each were in certain respects similar but not identical and the results obtained by different methods, in the majority of instances, were mutually corroborative. For clearness it may be advantageous to sketch separately the progress brought about by each individual method.

CONCLUSIONS BASED ON VAN'T HOFF'S SUPERPOSITION THEORY

First phase

The pioneer work on the application of van't Hoff's theory for the purpose of bringing out configurational relationships was done by C. S. Hudson. A complete review of this work will not be attempted in this place for several reasons. It would occupy more space than the scope of the article permits. To some extent, it is being reviewed by Hudson himself. In this sketch only an outline of Hudson's method of reasoning is given.

The first paper by Hudson on this subject bears the title "The Significance of Certain Numerical Relations in the Sugar Group" and is concerned principally with the configuration of carbon atom (1) of the simple sugars and of their glycosides. The deductions made in that paper are based on two fundamental principles: one is that of van't Hoff, postulating that the molecular rotation of a substance with more than one asymmetric group is equal to the algebraic sum of the rotations of the individual groups. The second refers to the structure of simple sugars. The discovery of α- and β-isomers of simple sugars and of their glycosides led E. Fischer and other sugar chemists to accept for simple sugars the structure suggested by Tollens and now known as the oxidic structure, namely,
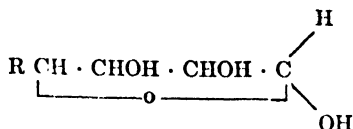
$$R\ CH \cdot CHOH \cdot CHOH \cdot C \overset{\displaystyle H}{\underset{\displaystyle OH}{\diagup \diagdown}}$$

Here R stands either for H, (C_nH_{2n+1}) or for $CH_2OH(CHOH)_n$. Hudson pointed out that the molecular rotation of a simple sugar may be regarded as the algebraic sum of the rotations of carbon atom (1) and of that of the rest of the molecule. Thus, designating the α-isomer

$$R \cdot CH \cdot CHOH \cdot CHOH \cdot C \overset{H}{\underset{OH}{<}}$$
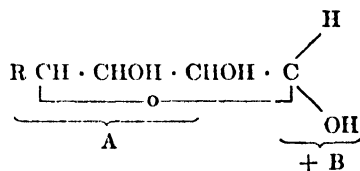
the β-isomer will have to be expressed

$$R \cdot CH \cdot CHOH \cdot CHOH \cdot C \overset{OH}{\underset{H}{<}}$$
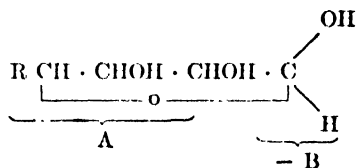
Thus, the sum of the molecular rotation represents the value of 2 A and the difference that of 2 B.

By the use of this method, Hudson succeeded in establishing important relationships concerning the configuration of carbon atom (1) of simple sugars and of their glycosides; later, he extended the method for exploring the structure of several di- and trisaccharides as regards the α- or β-character of their glycosidic unions. The work has been both stimulating and important.

Second phase

This phase relates to stereochemical relationships of hydroxy acids. In search for a clue to the solution of the problem of the allocation of the amino group in 2-aminohexonic acids, P. A. Levene was led to test whether the superposition theory of van't Hoff holds also for hexonic acids. The reasoning of Levene was analogous to that of Hudson. The molecular rotation of a hexonic acid may be regarded as the sum of rotations of two parts: one consisting of carbon atoms (1) and (2) and the other

including carbon atoms (3), (4), (5) and (6). Thus, taking a pair
of epimeric hexonic acids, each isomer may be represented as
follows:

$$
\begin{array}{c}
\mathrm{H} \\
| \\
\mathrm{CH_2OH \cdot CHOH \cdot CHOH \cdot CHOH \cdot C{-}COOH} \\
\underbrace{}_{A} \qquad | \\
\mathrm{OH} \\
\underbrace{} \\
+ \mathrm{B}
\end{array}
$$

$$
\begin{array}{c}
\mathrm{OH} \\
| \\
\mathrm{COOH \quad C \cdot CHOH \cdot CHOH \cdot CHOH \cdot CH_2OH} \\
| \qquad \underbrace{}_{A} \\
\mathrm{H} \\
\underbrace{}_{-\,\mathrm{B}}
\end{array}
$$
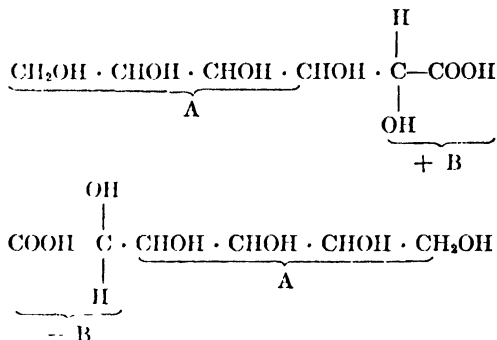
Here then the sum of the molecular rotations of the two acids
is equal to 2A, and the difference to 2B.

Analysis of the data published by different writers but prin-
cipally by Nef on the rotations of metal salts, alkaloidal salts
and of phenylhydrazides of a number of sugar acids revealed
the regularity in the direction of rotation of the carbon atoms
(2) of the entire group of substances, namely, it was found that
in all acids which had the allocation of the hydroxyl of carbon
atom (2) as in the d-gluconic acid, the rotation of B was to the
right and in those with the configuration of carbon (2) as in
d-mannonic acid, the rotation of B was to the left. Later in
coöperation with G. M. Meyer, Levene prepared a series of metal
salts of sugar acids and later a series of phenylhydrazides. The
original conclusions of Levene were substantiated by the more
comprehensive analysis. Hudson also lent his attention to the
optical behavior of sugar acids and noted that the rotation of
B in the phenylhydrazides of sugar acids was quantitatively
higher than that of A, and that therefore the direction of rota-
tion of carbon atom (2) is in the same direction as that of the
phenylhydrazide. Hence, according to Hudson, it was not
necessary to possess a pair of epimers in order to determine the
direction of rotation of carbon atom (2). Later Weerman and
also Hudson and his co-workers directed their attention to the

amides of sugar acids. Hudson further extended his observations to acids of simpler structure, namely, to tartaric and malic, the configurations of which were established by chemical means and he found that also in the case of these acids the rule held, namely, d-tartaric acid amide

$$
\begin{array}{ccc}
 & OH & H \\
CONH_2 - & C - C - & CONH_2 \\
 & H & OH
\end{array}
$$
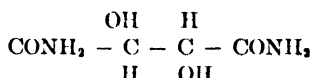
in agreement with the prediction rotated to the right and l-malic

$$
\begin{array}{cc}
 & OH \\
CONH_2 - CH_2 - & C - CONH_2 \\
 & H
\end{array}
$$
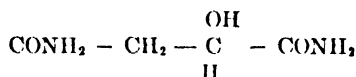
to the left. Hudson then applied the rule to levo-mandelic acid and attributed to it the configuration of the l-acids. Freudenberg, however, later modified the rule of Hudson to read that all such acids are to be designated as d-acids of which the amides have a higher dextro-rotation than the free acids. When so formulated, the rule held for all acids of known configuration and also for mandelic acid.

The case of levo-mandelic acid is important for the following reason. Mandelic acid is levo-rotatory ($-153°$) and forms a levo-rotatory amide ($-95.5°$) and hence, according to the rule of Hudson, should be regarded as an l-acid. On the other hand, hexahydromandelic acid obtained by the hydrogenation of levo-mandelic acid is levorotatory ($-26.6°$) and forms a dextrorotatory amide. Thus, according to the original rule of Hudson, different configurations should be assigned to the two acids but according to the rule as modified by Freudenberg, the same configuration of d-acids is assigned to both.

Thus, in regard to the configuration of hydroxy-acids, the work of Levene, Hudson, Weerman and Freudenberg led to the formulation of definite rules which permit the determination of the configuration of a hydroxy acid on the basis of its optical behavior. It must be emphasized, however, that all the work thus far reviewed was concerned principally with developing a physical method for ascertaining configurational relationships of

hydroxy derivatives only. The next task was to discover a way for coördinating configurations of amino and hydroxy derivatives. The work of Levene on hexosaminic acids had that aim. Similar was the aim of the work of Clough. The methods employed by Clough were the outgrowth of much important work on the relationship of chemical structure and optical rotation which was done by many very prominent chemists, namely, Frankland, Armstrong, McKenzie, Patterson, Pickard and Kenyon and others. The principal contributions bearing on the topic under discussion are reviewed in the following section.

INFLUENCE OF EXTERNAL CONDITIONS SUCH AS TEMPERATURE AND CHARACTER OF SOLVENT AND OF SUBSTITUTION ON OPTICAL ROTATION

It may be well to begin the survey of the work on this topic by reference to the publication by Frankland and Wharton in 1896. The investigation was concerned with the influence of chemical structure on the optical activity. In that, the rotatory powers of dibenzoyl and ditoluyltartrates are discussed. The unexpected observation made in the course of the work is contained in the following quotation: "This is a very remarkable series of rotations, exhibiting, as it does, a phenomenon which, as far as we are aware, has not hitherto been observed, namely, the passage through a maximum in the change of rotation, brought about by change of temperature, or, in other words, a change in the sign of the sensitiveness of the rotation due to the temperature."

The results are given in table 1.

In a more extensive way the influence of solvent and of temperature on rotation was investigated by T. S. Patterson. At the outset of his work, Patterson was engaged in searching for the causes of the variation of the rotatory power of a substance n different solvents. The method employed by this author onsis ted in comparing the curves expressing the changes of rotations with respect to changes of temperature. Patterson discarded the then-prevailing theory that the cause of the variation of rotation was due to the differences in the state of aggrega-

tion in different solvents and instead was inclined to accept the view that the principle variable was the molecular solution volume. Soon, however, the work assumed a broader aspect, namely, the search for such peculiarities or singular points in the temperature rotation (T.R.) curves which could offer a basis of comparison between structurally related substances. Patterson

TABLE 1

Rotation of ethylic dibenzoyltartrate

(Length of polarimeter tube in each case was 44 mm.)

$$\text{At} \quad 1.3° \ [\alpha]_D = \frac{-30.06°}{0.44 \times 1.2121} = -56.36°; \ [\delta]_D = -477.5.$$

$$\text{At} \quad 18.0° \ [\alpha]_D = \frac{-31.29°}{0.44 \times 1.1979} = -59.36°; \ [\delta]_D = -499.0.$$

$$\text{At} \quad 38.0° \ [\alpha]_D = \frac{-32.06°}{0.44 \times 1.1809} = -61.70°; \ [\delta]_D = -514.0.$$

$$\text{At} \quad 41\ 0° \ [\alpha]_D = \frac{-32\ 10°}{0.44 \times 1\ 1758} = -62.05°; \ [\delta]_D = -515\ 0.$$

$$\text{At} \quad 53.5° \ [\alpha]_D = \frac{-32\ 00°}{0.44 \times 1.1677} = -62.28°; \ [\delta]_D = -514\ 5.$$

$$\text{At} \quad 60.0° \ [\alpha]_D = \frac{-31\ 85°}{0.44 \times 1.1622} = -62.28°; \ [\delta]_D = -513.0.$$

$$\text{At} \quad 77.5° \ [\alpha]_D = \frac{-31.37°}{0.44 \times 1.1472} = -62.15°; \ [\delta]_D = -507.0.$$

$$\text{At} \quad 100.0° \ [\alpha]_D = \frac{-30.16°}{0.44 \times 1.1280} = -60\ 77°; \ [\delta]_D = -490.5.$$

$$\text{At} \quad 109.5° \ [\alpha]_D = \frac{-29.51°}{0.44 \times 1.1199} = -59.89°; \ [\delta]_D = -481.0.$$

$$\text{At} \quad 136.5° \ [\alpha]_D = \frac{-27.38°}{0.44 \times 1\ 0970} = -56.72°; \ [\delta]_D = -450.0.$$

$$\text{At} \quad 182.5° \ [\alpha]_D = \frac{-24\ 03°}{0.44 \times 1.0571} = -51.66°; \ [\delta]_D = -399.5.$$

was impressed by the fact first noted by Frankland and Wharton that every T.R. curve had a sinuous form exhibiting a maximum and a minimum. This author then concentrated his attention on the position of the maximum point with the change of concentration and of temperature. Figure XXVII presents the results of measurements of the molecular rotation of aqueous solutions of potassium ethyltartrate. In these experiments the

position of the maximum varied with concentration of the solute. It varied also with the solvent and with the character of the chemical group introduced into the tartaric acid.
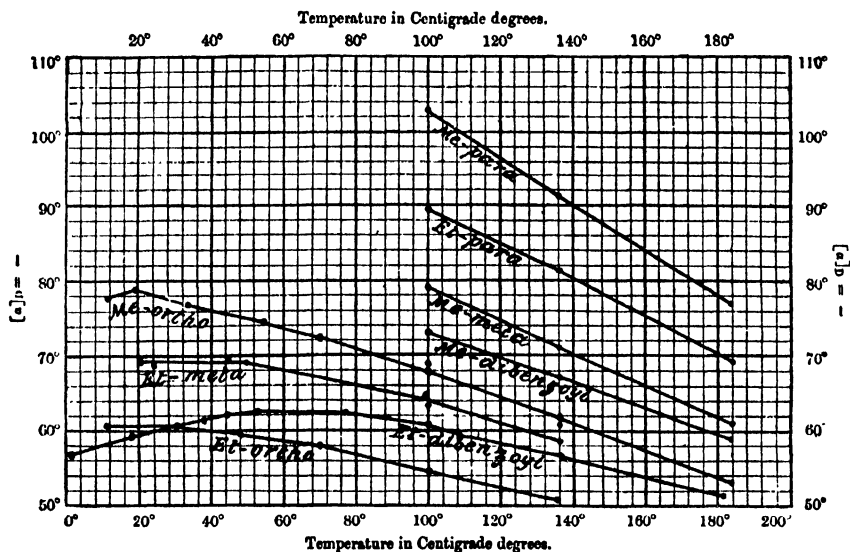
FIG. XXVI. INFLUENCE OF TEMPERATURE ON THE SPECIFIC ROTATION OF METHYLIC AND ETHYLIC DITOLUYLTARTRATES, AND OF METHYLIC AND ETHYLIC DIBENZOYLTARTRATES
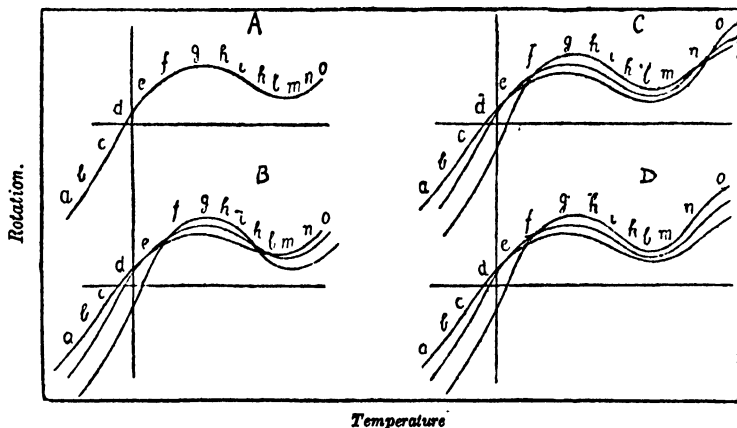
FIG. XXVII

Patterson, after work which extended over many years and which embraces a great number of substances, came to the conclusion that closely related chemical substances such as esters of tartaric acid exhibit similar temperature rotation curves, although the maximum rotation may occur at different temperatures and at different rotations.

The significance of the temperature rotation curve as a basis of comparison of configurationally similar substances was further demonstrated by Pickard and Kenyon in a long series of investigations on the derivatives of simple secondary carbinols.

As experience and data accumulated, it became evident that another important factor had to be considered in comparing configurationally related substances, namely, the color of the light employed for the measurement of the rotation. In this connection a very important discovery was made by Armstrong and Walker. These authors suggest that the specific rotations of substances for light of different refrangibilities can be arranged diagrammatically and, what they term a "characteristic diagram" is formed by configurationally related substances. Armstrong and Walker describe the construction of the diagram in the following words:

To construct the diagram characteristic of a substance, a reference line is drawn with a slope of unity and on this are plotted the various specific rotations of light of any of the refrangibilities observed. The points for other refrangibilities are then plotted on the ordinate passing through the points previously located on the reference line. The observations may be those made either in different solvents or at different concentrations.

Figure XXVIII represents the characteristic diagram for d-fructose in different concentrations. The measurements were made by Armstrong and Walker. In Figure XXIX specific rotations are plotted as functions of solvent.

The application of rotatory dispersion was further advanced by the very important work of T. M. Lowry who demonstrated that for the majority of organic substances, the rotatory dispersion can be expressed by Drude's formula

$$\alpha = \frac{K}{\lambda^2 - \lambda^2_0} \tag{I}$$

He termed the form of dispersion which can be expressed by this formula, "simple dispersion," in distinction from "complex dispersion" which could not be expressed by the simple formula
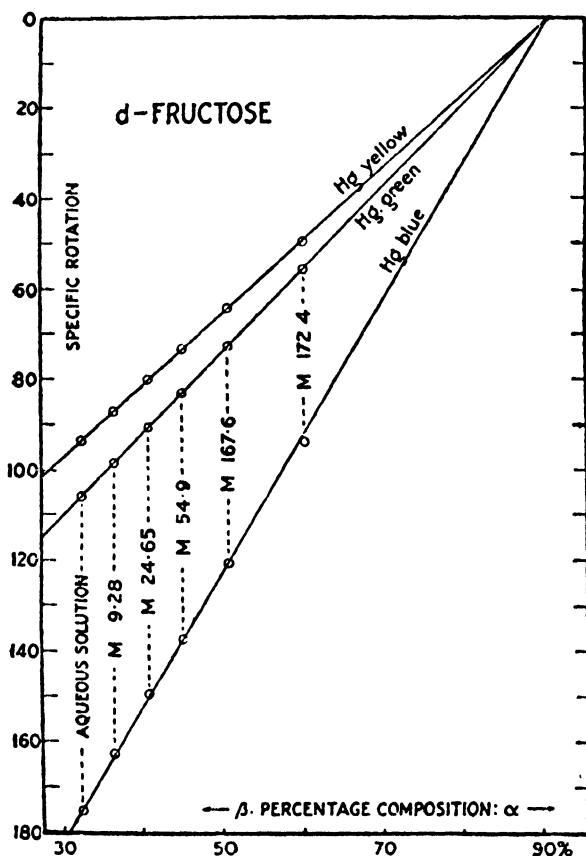
FIG. XXVIII. CHARACTERISTIC DIAGRAM OF d-FRUCTOSE

Equilibrium between α and β forms altered by the addition of alcohol to the aqueous solution. Reference color, Hg green.

and which required for its expression the two membered formula containing four constants:

$$\alpha = \frac{K_1}{\lambda^2 - \lambda^2_1} - \frac{K_2}{\lambda^2 - \lambda^2_2} \tag{II}$$
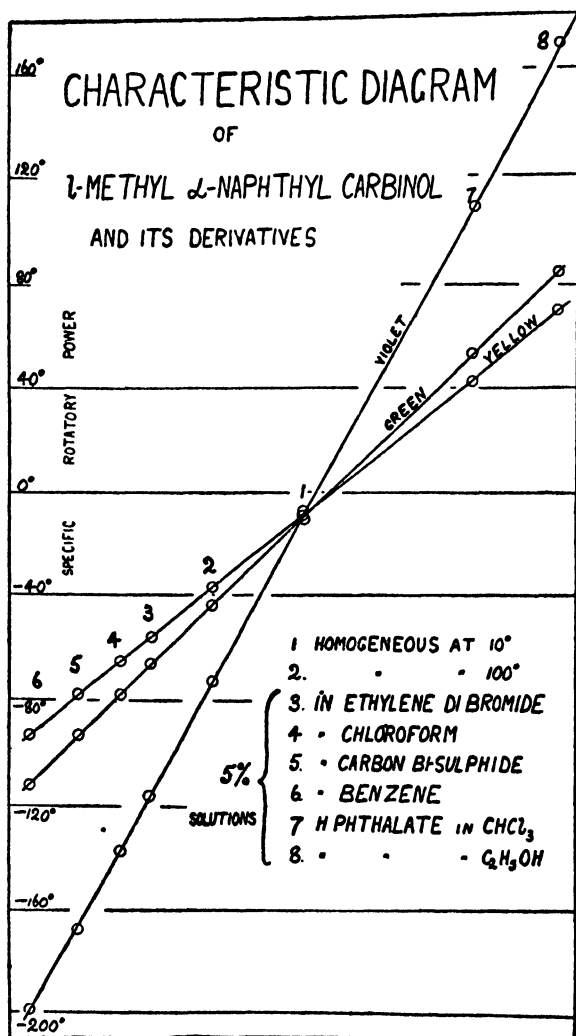
Fig. XXIX. Characteristic Diagram for 1-Methyl-α-Naphthyl Carbinol
and its Derivatives
The measurements were made by Pickard and Kenyon

It is evident that K, in all cases where formula (I) holds for lights of all refrangibilities, is independent of the wave length, and hence K- the rotation constant, expresses better the rotatory

properties of a substance than the value of the specific rotation at one given wave length.

Very useful information was obtained when rotatory dispersion was measured at varying temperatures. Namely, it was observed that certain substances exhibited complex dispersion up to a certain range of temperature changes and then followed the simple law. This indicates that the complexity of the solution is smaller at the temperatures exhibiting the simple dispersion and hence comparisons made at those temperatures are more serviceable.

To sum up, the studies in temperature rotation changes and those in rotatory dispersion, aimed at a method of expressing those rotatory powers of a substance which were, as far as possible, free from external influences. The methods here reviewed were particularly useful in correlating the configurational relationships of carbinols but were also applied to work which constitutes the main theme of this review and to which the following two sections are devoted.

CONFIGURATIONAL CORRELATION BETWEEN AMINO ACIDS AND HYDROXY ACIDS

Chronologically, after the discovery of Walden Inversion, the systematic effort of correlating the configuration of amino acids with hydroxy acids was made by Levene, but the publication of Clough had a more comprehensive scope and for this reason, the discussion will begin with a review of his article, published in 1918. The principles developed by Frankland, Patterson, Pickard and Kenyon were accepted by Clough and made the basis for a comparison of the configurational relationships of hydroxy, amino and halogen acids.

Hydroxy acid

Clough began his discussion by the analysis of the influences of external conditions such as temperature, solvent and certain substituents on a series of acids of known configuration, namely, on levo-lactic, levo-glyceric, dextro-malic and dextro-tartaric. These acids, as developed in the earlier part of this review, are

configurationally identical and because of their relationship to d-glucose may be designated d-acids.

Clough then extended his analysis to hydroxy acids of which the configuration had not been known. Thus he examined the

TABLE 2

The influence of sodium bromide on the optical rotatory power of levomalic acid, dextro-tartaric acid, methyl-levo-lactate, methyl-levo-malate, and methyl-dextro-tartrate in methyl alcoholic solution

COMPOUND	$[\alpha]_{gr.}^{15}$ (IN METHYL ALCOHOL C = 10)	$[\alpha]_{gr.}^{15}$ (IN METHYL ALCOHOLIC SODIUM BROMIDE N. C = 10)
Levo-malic acid	−5.9	+21.8°
Dextro-tartaric acid	+2.6	−9 0
Methyl-levo-lactate	+5.4	−5 8
Methyl-levo-malate	−9.4	+9.1
Methyl-dextro-tartrate	+2.7	−12.6

TABLE 3

The influence of sodium haloids on the optical rotatory powers of dextro-β-phenyl-lactic acid and methyl-dextro-β-phenyl-lactate in solution

COMPONENT	SOLVENT	$\frac{\Lambda}{C}$	$t°$	$\alpha_{gr.}^{t}$ $_{(l=2)}$	$[\alpha]_{gr.}^{t}$
Dextro-β-phenyl lactic acid	Water	2.505	20°	+1.28°	+25.5
	Aqueous sodium chloride (4N)	0 665	20°	+0.18	+13.5
	Methyl alcohol	10.0	20°	+4.20	+21.0
	Methyl alcoholic sodium bromide (N)	10.0	20°	−0.41	−2.0
Methyl-dextro-β-phenyl lactate	Methyl alcohol	10.0	18°	−0.90	− 4.5
	Methyl alcoholic sodium bromide	10 0	18°	−4.46	−22.3

influence of sodium chloride (or bromide) on dextro-β-phenyl lactic acid and its methyl ester. On the basis of similarity of the action of these salts on this acid and on the derivatives of levo-malic, levo-lactic and dextro-tartaric acids, he assigned to

dextro-β-phenyl lactic acid the configuration of the d-series. Of the many tables relating to the hydroxy acids the two pertaining to this case are given by way of an illustration of Clough's procedure.

In a similar way the behavior of levo-α-hydroxyisohexoic, levo-α-hydroxyglutaric and levo-α-hydroxyisovaleric acids was analyzed.

The conclusions regarding the configurations of hydroxyacids suggested by Clough are: "levo-lactic acid, levo-glyceric acid, dextro-malic acid, dextro-α-hydroxy butyric acid, dextro-α-hydroxyisovaleric acid, dextro-α-hydroxyisohexonic acid, dextro-α-hydroxyglutaric acid and dextro-β-phenyl lactic acid all possess the same relative configuration as dextro-tartaric acid."

2-Amino acids

Clough then proceeded to investigate the influence of inorganic salts and of different solvents on the optical rotatory power of amino acids.

The following tables contain the data of such information as was obtained by Clough or as collected by him from literature.

Applying to the analysis of the optical behavior of amino acids the same mode of reasoning as was used in connection with the hydroxy acids, Clough formulated the following conclusion regarding the configuration of naturally occurring amino acids.

Naturally occurring amino acids, commonly denoted as dextro-alanine, levo-serine, levo-aspartic acid, dextro-valine, levo-leucine, dextro-isoleucine, dextro-aminobutyric acid, dextro-glutamic acid, levo-phenyl-alanine, and levo-tyrosine all possess the same configuration. The configuration of these compounds has been denoted by the symbol "l."[1]

In a similar manner, Clough has analyzed the behavior of α-halogen acids. In connection with this class of compounds,

[1] Clough denotes by "d" such acids that have the configuration of d-tartaric acid and as "l" those having the configuration of levo-tartaric acid. The present writer suggests the indication of the direction of rotation by the words "dextro," or "levo," and those having the configuration of d-tartaric acid as d-acids. This practice would be in harmony with the designations now in use in the sugar acids.

TABLE 4

The influence of inorganic salts on the optical rotatory power of d-glutamic acid in aqueous solution

SOLVENT	p	d^{25}	$\alpha^{25}_{gr.}$ ($l = 4$)	$[\alpha]^{25}_{gr.}$
Water.	1 50	1 003	+0 80°	+13.3°
Aqueous sodium chloride (N)	1 50	1 043	0 90	14.4
Aqueous sodium chloride (4N)	1 51	1.152	1 10	15 8
Aqueous potassium chloride (N)	1 53	1 050	0 95	14.8
Aqueous barium chloride (N)	1 53	1 092	0 96	14 4
Aqueous barium bromide (4N)	1.51	1.500	1.64	18.1
Aqueous sodium hydroxide (1 mol.)	12 25	1.075	−1 88	−3 6
Aqueous sodium hydroxide (2 mols.)	6.55	1.050	+3.22	+11.7
Aqueous hydrogen chloride (1.5 mols.)	8.75			+37.4

TABLE 5

The influence of solvents on the optical rotatory power of ethyl l-aspartate

SOLVENT	c	$\alpha_{gr.}^{18} (l = 2)$	$[\alpha]_{gr.}^{18}$
None..	$10\ 92°$	$-6\ 34° (l = 0\ 5)$	$-11.7°$
Benzene...	$11\ 02$	$-2\ 75$	$-12\ 6$
Chloroform.....................................	$20\ 0$	$-2\ 13$	$-9\ 7$
Acetone*.......................................	$21\ 7$	$-3\ 50$	-8.8
Water...	$12\ 25$	$+1\ 83$	$+4.2$
Water...	$10\ 81$	$1\ 03$	4.2
Aqueous sodium chloride (4N)................	$14\ 50$	$1\ 44$	6.7
Aqueous barium bromide (4N)................	$13\ 21$	$3\ 34$	11.5
Aqueous calcium chloride (5N)...............	11.37	$3\ 84$	14.5
Aqueous hydrogen chloride (N)..............		$2\ 73$	12.0
Methyl alcohol.................................	20.0	$\alpha_{gr.}^{20} -0.19$	$[\alpha]_{gr.}^{23} -0.5$
Methyl-alcoholic sodium bromide (N).......	$20\ 0$	$\alpha_{gr.}^{21} +1.72$	$[\alpha]_{gr.}^{20} +4.3$

* Ethyl l-aspartate reacts with acetone, the rotation changing from $\alpha_{gr.} -3.50°$ to $\alpha_{gr.} -56.6°$ ($c = 20$) in fifteen hours.

TABLE 6

The optical rotatory powers ($[\alpha]_D^{18}$) of α-amino acids and of certain derivatives from them

AMINO-ACID	WATER	HYDRO-CHLORIC ACID	BENZOYLAMINO-ACID (IN KOH, AQ)	AMINOACYLGLYCINE (IN WATER)	GLYCYLAMINO-ACID (IN WATER)	HYDANTOIN*
d-Alanine[1]	+2.7°	+14.3°	+36 5°	+50 2°	−50 0°	+50.6° (water)
l-Serine[2]	−6.8	+14.4	+43 6 (in NaOH, aq.) (p-nitrobenzoyl)	—	—	—
l-β-Chloro-α-aminopropionic acid[3]	−15.5	+0 9	—	—	—	—
d-α-Aminobutyric acid[4]	+8.0	+19.6	+30 7 (in NaOH, aq.)	+86.4 (K)	−20 3	—
d-Valine[5]	+6.4	+28 7	—	+26.8 (A & C) +90	−19 7	−97.5 (phenyl-hydantoin in alcohol).
d-α-Aminohexoic acid[6]	—	+23 0	+21 9	—	—	—
l-Leucine[7]	−10.3	+15 6	+6 6 (in NaOH, aq.)	+85 5	−35 0	−68.2 (in NaOH, aq.)

* Hydantoins, Dakin & Dudley, J. Biol. Chem., 1913, 17, 29; 1914, 18, 48; T., 1915, 107, 434.
1 Fischer, Ber., 1905, 38, 2914; 1906, 39, 453; 1907, 40, 943.
2 Fischer and Jacobs, Ber., 1906, 39, 2942; Fischer and Raske, Ber., 1907, 40, 3717.
3 Fischer and Raske, loc. cit.
4 Fischer and Mouneyrat, Ber., 1900, 33, 2383; Koelker, Zeitsch. physiol. Chem., 1911, 73, 312; Abderhalden and Chang, ibid., 1912, 77, 471.
5 Fischer, Ber., 1906, 29, 2320; Fischer and Scheibler, Annalen, 1908, 363, 136.
6 Fischer and Hagenbach, Ber., 1901, 34, 3764.
7 Fischer, Ber., 1900, 33, 2370; Ber., 1906, 39, 2893; Fischer and Steingroever, Annalen, 1909, 365, 167.

P. A. LEVENE

TABLE 7

The optical rotatory powers $([\alpha]_D^{20})$ of α-amino-acids and of certain derivatives from them

AMINO-ACID	WATER	HYDRO-CHLORIC ACID	BENZOYLAMINO-ACID (IN KOH, AQ)	AMINO-ACYLGLY-CINE (IN WATER)	GLYCYLAMINO-ACID (IN WATER)	HYDANTOIN*
d-iso Leucine[8].............	+11 3°	+40.6°	+26.4° (in NaOH, aq.)	+33 6°	-14.7°	—
l-Asparagine[9].............	-4 9	+28.5	—	—	-6.4	—
l-Aspartic acid[10]........	+4 3	+25 7	+37 4	—	+11.1	-125 (in NaOH, aq.)
d-Glutamic acid[11]........	+9 9	+30 8	+18 7	—	-6.3	-79 (in NaOH, aq.)
l-Phenylalanine[12]........	-35 3	-7 1	+17.1	+54.2	+41.4	-96.4 (in 50 per cent alcohol).
l-Tyrosine[13].............	—	-8.6	+19 2	—	—	-143 (in NaOH, aq.)

* Hydantoins, Dakin and Dudley, J. Biol. Chem., 1913, **17**, 29; 1914, **18**, 48; T., 1915, **107**, 434.

[8] Locquin, Bull. Soc. chim., 1907 [iv], **1**, 595; Abderhalden, Hirsch, and Schuler, Ber., 1909, **42**, 3394.

[9] Fischer and Koenigs, Ber., 1904, **37**, 4585.

[10] Fischer, Ber., 1899, **32**, 2451; Fischer and Fiedler, Annalen, 1910, **375**, 181.

[11] Fischer, Kropp, and Stahlschmidt, Annalen, 1909, **365**, 189.

[12] Fischer and Mouneyrat, loc. cit.; Fischer and Schoeller, Annalen, 1907, **357**, 1.

[13] Fischer, Ber., 1899, **32**, 3638.

the available data were very meagre. Nevertheless, Clough felt justified in drawing the following conclusion:

The dextrorotatory α-halogen acids which have been isolated are assumed to be configurationally similar compounds. A comparison of the rotatory powers of the optically active α-bromoacylamino acids with those of the α-aminoacylamino acids leads to the view that the halogen acids mentioned above are configurationally related "l" amino-acids.

Thus, according to Clough, the naturally occurring amino acids have the configurations of l-tartaric acid and the dextro halogen acids have the same configurations. Clough, however, states that further investigations are desirable in order that a definite decision may be reached.

Simultaneously with Clough, Karrer, in coöperation with Kaase, measured the optical rotatory dispersion of dextro-glutamic acid, and of several of its derivatives, the ethyl ester, levo-chloroglutaric and dextro-hydroxyglutaric. The amino acid, the hydroxy acid and several other derivatives exhibited a rise in dextrorotation with the decrease in the wave length; the chloroderivative exhibited an increase to the left. Karrer and Kaase drew the conclusion that the hydroxy and the amino acids examined by them were configurationally related, whereas the levo-chloroacid was enantiomorphously related to the former two. With respect to the amino and chloroacid, the conclusions of Karrer and Kaase coincided with that of Clough.

Very recently, Freudenberg and Rhino measured the rotation constant of several derivatives of dextro-alanine with similar derivatives of dextro-lactic acid. The calculations were made by the Ackerman formula which is Drude's rotatory dispersion formula. Its applicability for the measurement of rotatory dispersion of organic compounds was first demonstrated by Lowry. Table 8 contains the results of the observations of Freu-denberg and Rhino.

On the basis of these results, Freudenberg and Rhino consider dextro-alanine and dextro-lactic acids configurationally similar and denote the two acids l-acids.

Thus, practically every one of the methods introduced by Frankland, Patterson, Armstrong, Pickard and Kenyon for the study of stereochemical relationships was made use of in the investigations of configurational relationships between hydroxy acids, halogen acids and amino acids.   Thus far, the conclusions have been mutually corroborative.

TABLE 8

	K_M NATURAL (DEXTRO) ALANINE	K_M DEXTRO LACTIC ACID
1. Amide of the benzoyl derivative.................	$< +29$	$+36$
2. Ethyl ester benzoyl derivative...................	$+3$	$+10.5$
3. Methyl ester benzoyl derivative	$0 \ (\pm 1)$	$+7.5$
4. Ethyl ester of the hexahydrobenzoyl derivative...	$-19 \ (\pm 4)$	-15
5. Ethyl ester of the acetyl derivative..............	-22	-25
6. Amide of Toluolsulfo derivative.................	$-26 \ (\pm 8)$	$-28 \ (\pm 3)$
7. Ethyl ester Toluolsulfo derivative..	-26	-39

THE INFLUENCE ON THE OPTICAL ROTATION OF THE CHANGE OF POLARITY OF ONE OF THE GROUPS ATTACHED TO THE ASYM- METRIC CARBON ATOM BROUGHT ABOUT WITHOUT THE PROCESS OF SUBSTITUTION

It was pointed out in the early section of this review that the correlations in the group of hydroxy acids were to a large extent established by methods of pure organic chemistry.   Also those that have not yet been correlated by these methods undoubtedly will be some day in the not distant future.   Many of the amino acids have been mutually correlated by purely chemical methods. It is not impossible that the halogen substituted acids will be mutually correlated by such methods.   However, there is little hope that hydroxy, amino and halogen acids will be correlated by purely chemical methods.   The cause of the difficulty lies in the phenomenon of Walden Inversion.   When the condition under which the Inversion takes place will be discovered, then the correlation between the configuration of the three groups of substances will become apparent of itself.   The work on Walden

Inversion done up to the present remains without practical value for the investigations into configurational relationships. Recently, Levene has undertaken a series of investigations which promises to throw some light on the circumstances under which the phenomenon of Walden Inversion occurs. The plan of the work consists in observing the changes in the optical activity of a substance which are brought about by changes in the polarity of one group attached to the asymmetric carbon atom when the change is accomplished without substitution. Levene, in co-operation with Mikeska, observed the changes in the optical behavior of secondary thioderivatives and of the corresponding sulfonic acids. The results of the observations are the following. In the derivatives of normal secondary alcohols, the changes in direction of rotation are as follows:

$$
\begin{array}{ccc}
\quad\text{H} & \quad\text{H} & \\
\quad| & \quad| & \\
R_1 - C - R_2 \text{ by III} \longrightarrow & R_1 - C - R_2 \longrightarrow & \\
\quad| & \quad| & \\
\quad\text{OH} & \quad\text{X} &
\end{array}
$$
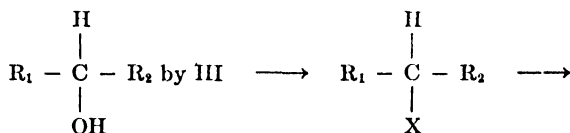
dextro-rotatory.   Substitution, (X stands for halide) levo-rotatory.

$$
\begin{array}{cc}
\quad\text{H} & \quad\text{H} \\
\quad| & \quad| \\
R_1 - C - R_2 \longrightarrow & R_1 - C - R_2 \\
\quad| & \quad| \\
\quad\text{SH} & \quad\text{SO}_2 \\
& \quad| \\
& \quad\text{CH}
\end{array}
$$

Substitution   change without
dextro-rotatory   substitution
                     levo-rotatory.

Thus, in this group of substances, the last change of the direction of rotation is brought about under conditions which exclude the possibility of a Walden Inversion and therefore, one is justified in concluding that normal aliphatic dextrorotatory

secondary alcohols are configurationally related to the levorotatory halides and that the above conversion of the alcohol into the halide has taken place without Walden Inversion.

Levene and Mikeska then extended their observations to α-substituted acids.

In this group of substances the change from the thio to the sulfonic acid derivative is not accompanied by the same change of rotation that was characteristic of the derivatives of the normal secondary alcohols. A decrease in dextro-rotation, perhaps, is exhibited by the sulfonic acid derivatives. This needs confirmation. The important fact, however, is that in the thio acid and in the sulfonic acid, there is observed the same character of change of rotation when the acid is converted into a metallic salt. Thus, dextro-thiolactic acid forms a levorotatory sodium salt, and the configurationally related sulfopropionic acid shows a similar change of rotation when it is transformed into a metallic carboxylic salt. The results of the measurements are given in table 9.

TABLE 9

Optical activity of the salts of thio and sulfo acids

SUBSTANCE	FREE ACID $[M]_D$	MONO-SALT $[M]_D$	DI-SALT $[M]_D$	TRI-SALT $[M]_D$
l-Xanthopropionic acid	+107.68°	+45 05°		
l-Thiolactic acid	+58.98°	−5.58°	+7.32°	
l-Sulfopropionic acid	+13.76°	+12 84°	−3.28°	
l-Xanthosuccinic acid	+95.05°	+43.86°	+8.65°	
l-Thiosuccinic acid	+73.06°	+41.58°	+48.57°	+41.09°
l-Sulfosuccinic acid	+44.25°	+43.43°	+29.22°	+25.67°
d-Sulfobutane	−4.38°	−6.29°		

At first glance the results summarized in this table seem confusing. Thus the dextrorotatory thiolactic acid forms a levorotatory monobasic salt. It behaves in this respect similarly to dextro-lactic acid. The direction of rotation, however, is again changed when a second equivalent of sodium hydroxide is added to the solution. Thus the neutral salt is dextrorotatory. In the sulfopropionic acid the direction of rotation is unaltered

when the acid is converted into a monobasic salt, and is reversed in the dibasic salt. This apparently puzzling difference in the behavior of the two substances, however, can be readily explained. In dextro-thiolactic acid

$$CH_3 - \overset{\displaystyle SH}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}} - COOH$$
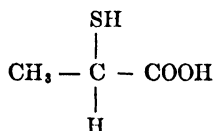
the carboxyl is the stronger acidic group. When the hydrogen of this group is replaced by a metal ion, the substance behaves as dextro-lactic acid, namely, the salt is levorotatory. When a second equivalent of the base is added, it replaces the hydrogen atom of the sulfide rest and then the direction of the rotation turns to the right.

In the sulfopropionic acid

$$CH_3 - \overset{\displaystyle OH}{\underset{\displaystyle H}{\overset{|}{\underset{|}{\overset{\displaystyle SO_2}{\underset{|}{\overset{|}{C}}}}}}} - COOH$$
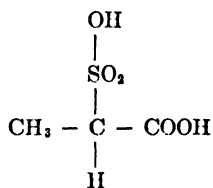
the stronger acidic group is the SO_2OH rest. The neutralization of this group brings about a slight change in the direction toward the left, as is the case when the thio group is neutralized in dextro-thiolactic acid. When a second· equivalent of base is added, this forms a salt with the carboxyl group and then the direction of the rotation is shifted to the left as is the case when the carboxyl group is neutralized in the dextro-thiolactic or in the dextro-lactic acids.

In a similar way, the changes in rotations of the thio- and sulfosuccinic acids may be analyzed.

These observations are instructive inasmuch as the configurational relationships of the substances are known from the methods of their preparation and hence the observations show that substituted acids configurationally related exhibit similar changes

of optical rotation when the acids are converted into the metallic salts even though the polarity of one of the groups attached to the asymmetric carbon atom is changed. Thus, dextro-lactic acid and dextro-alanine should also be regarded as configurationally related for the reason that in both, the free acid has a higher dextrorotation than the metallic salt. The same conclusions regarding dextro-lactic acid and dextro-alanine were reached by Clough and by Freudenberg on other grounds. The evidence of Levene and Mikeska is more direct than that of the other writers.

THE STEREOCHEMICAL RELATIONSHIPS OF HEXOSES AND HEXONIC ACIDS TO 2-AMINOHEXOSES AND 2-AMINOHEXONIC ACIDS

Work on this problem was undertaken prior to any other systematic investigation into the configurational relationship of amino and hydroxy derivatives. The original plan of the work was a comprehensive one. It was hoped first to correlate the simple sugars and sugar acids with aminohexoses and hexosaminic acids, then to reduce the latter to α-amino acids and thus to establish the configuration of amino acids by purely chemical methods. Work on aminopentonic acids also was contemplated. Unfortunately, the attempts to reduce the 2-aminohexonic acids to optically active 2-aminocaproic acids were not successful. Nevertheless, the work on hexosamines and on aminohexonic furnished very important data for the elucidation of the configurational relationship of hydroxy and of amino acids.

The advantages which the sugar acids offer for the study of stereochemical relationships are the following: A pair of enantiomorphous substances differ from one another by only one property, the direction of the optical rotation. Two sugar acids enantiomorphous only with regard to carbon atom (2) differ, as a rule, in other physical properties in addition to the optical and often differ also in their chemical behavior. Furthermore, the acids can be reduced to the corresponding sugars, and these again differ markedly from one another. Thus, gluconic and mannonic acids are characterized not only by the optical behavior

of the free acids and their salts, amides, and phenylhydrazides, but also by their solubilities, their tendencies to form crystalline lactones, etc., and in addition, by the physical and chemical properties of glucose and of mannose to which they can be reduced respectively.

Levene and his co-workers synthetically completed the series of 2-aminohexonic acids (only one had been known prior to their work). Making use of the van't Hoff superposition theory in a manner similar to that applied by Hudson to sugars, they classified the eight d-2-aminohexonic acids into two groups, namely,

Group I	Group II
Chitosaminic	Epichitosaminic
Chondrosaminic	Epichondrosaminic
Levo-xylohexosaminic	Dextro-xylohexosaminic
Levo-ribohexosaminic	Dextro-ribohexosaminic

The substances in each group are configurationally related in regard to carbon atom (2). The substances in group I and group II are enantiomorphously related in regard to carbon atom (2). The basis for this classification is the comparison of the values of the optical rotations of carbon atom (2) in the hydrochlorides of the amino acids. The next problem was to establish the allocation of the amino groups in these acids. The configuration of carbon atom (2) in hexonic acids has been definitely established by chemical methods. It thus became necessary to establish the genetic relationships between the hexonic and the amino hexonic acids.

Table 10 represents the values and the direction of the rotation of carbon atom (2) in the hexonic and hexosaminic acids when the rotation of the hydrochlorides of the latter are compared with those of the phenylhydrazides of the former.

The similarity of the specific rotations is striking. However, this property alone is not sufficient to establish the configurational relationships of the two groups of substances. Therefore additional proof was needed. For this reason, the following points were investigated: first, the equilibrium between the two epimeric hexonic acids formed by the addition of prussic acid to a pentose;

second, the equilibrium between the corresponding two hexo-saminic acids formed through the addition of prussic acid to

TABLE 10

ACID HYDROCHLORIDES	$[\alpha]_D$ OF CARBON ATOM (2)	$[M]_D^{20}$	PHENYL-HYDRAZIDE	$[\alpha]_D$ OF CARBON ATOM (2)	$[M]_D^{20}$
Epichitosaminic...............	+12.5	+24 37	Gluconic	+14.25	+42.18
Chitosaminic.................	−12.5	−24 37	Mannonic	−14.25	−42.18
Dextro-xylohexosaminic.......	+12.5	+24.37	Gulonic	+14 25	+42.18
Levo-xylohexosaminic.........	−12 5	−24.37	Idonic	−14.25	−42.18
Epichondrosaminic............	+12 5	+24.37	Galactonic	+8.25	+24.42
Chondrosaminic....	−12.5	−24.37	Talonic	−8 25	−24.42
Dextro-ribohexosaminic........	+19.12	+37.28	Allonic	+20.8	+61.56
Levo-ribohexosaminic.........	−19.12	−37.38	Altronic	−20.8	−61.56

TABLE 11

FROM	ROTATION OF CARBON ATOM 2 IN PREDOMINATING FORM	FROM	ROTATION OF CARBON ATOM 2 IN PREDOMINATING FORM
Arabinose....................	Levo	Aminoarabinoside.........	Levo
Lyxose......................	Levo	Aminolyxoside.............	Levo
Xylose......................	Dextro	Aminoxyloside.............	Dextro
Ribose......................	Levo	Aminoriboside.............	Levo

TABLE 12

Chitosaminic acid.................................... 2-aminomannonic acid
Epichitosaminic acid................................ 2-aminogluconic acid
Chondrosaminic acid................................ 2-aminotalonic acid
Epichondrosaminic acid............................. 2-aminogalactonic acid
Dextro-d-xylohexosaminic acid....................... 2-aminogulonic acid
Levo-d-xylohexosaminic acid......................... 2-aminoidonic acid
Dextro-d-ribohexosaminic acid....................... 2-aminoallonic acid
Levo-d-ribohexosaminic acid......................... 2-aminoaltronic acid

amino-pentoses. The two equilibria were then compared and found as given in table 11.

On the basis of the analogies recorded in tables 10 and 11, the relationships as given in table 12 could be formulated.

Further, it was found that when chitosaminic acid was deaminized, it gave gluconic acid (as the 2-5 anhydro form) but not mannonic. This was in agreement with Fischer's assumption that on deamination of α-amino acids with nitrous acid, a Walden Inversion occurs.

If, in addition, it is remembered that it was customary to designate as "d-amino acids" all such acids which rotate to the right in hydrochloric acid solution, and as "d-hydroxy acids" all acids of which the salts rotate to the right, it will become evident how the relationships expressed in table 12 for a time seemed logical and correct.

Doubts as to the rationality of this mode of comparison came to the fore when the directions of rotations of carbon atom (2) were determined not from the behavior of the sugar acids but from that of the sugars themselves. On the basis of van't Hoff's superposition theory it is possible, as was shown by Hudson, to determine the direction of the rotation of carbon atom (2) of two epimeric sugars when the rotations of the α- β-forms of each are known. When, on the one hand, two hexoses, glucose and mannose, were taken for comparison and on the other hand, two 2-aminohexoses; chitosamine and epichitosamine (all may be taken in the form of pentacetates) then it was found that carbon atoms (2) in glucose and in chitosamine rotated in the same direction, namely, to the right, and mannose and epichitosamine both to the left. On the basis of these observations, chitosamine should be considered configuratively related to glucose, and epichitosamine to mannose. Thus, a contradiction arose between the conclusions reached on the basis of the optical rotations of the epimeric hexosaminic acids and those reached on the basis of the epimeric aminohexoses. Further inquiry became necessary in order that a decision could be reached in favor of one or the other conclusion. It may be added here that the preponderance of evidence was found in favor of the second of the two named relationships.

It was known from the work of Hudson and his co-workers that the difference in the molecular rotations of the α- and β-glucoses had a normal value, and from the calculations of

Hudson and Yanowsky and from the experimental work of Levene it was definitely proved that in the case of the α- and β-mannoses, the corresponding value was abnormal. Some time ago, Irvine prepared the α- and β-isomers of chitosamine hydrochloride and found that the difference of the molecular rotation of the two forms was normal and therefore suggested that chitosamine was configurationally related to glucose. This evidence alone would scarcely be sufficient to establish the configuration of chitosamine. The molecular rotations of sugars are determined largely by the character of the oxidic ring and it is possible that in a simple sugar and in the corresponding 2-amino sugar the predominating form may have a different ring structure.

However, though insufficient in itself, the conclusion of Irvine found confirmation in the above-mentioned result of the evaluation of the rotation of carbon atom (2) of chitose on the basis of the rotations of α- and β-chitose pentacetates and α- and β-epichitose pentacetates. A third point of evidence favorable to this conclusion is found in the consideration of the properties of epichitosamine. The difference of the optical rotations of the α- and β-forms of this sugar was found abnormal, resembling mannose in this respect, and if the structure of 2-amino mannose is attributed to epichitose, then the structure of 2-aminoglucose should be assigned to chitose. For this theory, then, three points of evidence have accumulated.

There still remained the puzzle of the discrepancy between the conclusions following from the observations made on the properties of the sugars and those of the acids. However, a wholly harmonious theory is reached when a different basis is chosen for connecting the configurations of hexonic and aminohexonic acids than the one taken for table 10.

A scrutiny of tables 13 and 14 showing the direction of the rotation of the hexonic acids in solution of dilute hydrochloric acid and the rotations of the metallic salts, phenylhydrazides or amides brings to light certain regularities. From these tables it is seen that all hexonic and all 2-aminohexonic acids can be

TABLE 13

Showing the specific rotations of the free acids and of their derivatives
(All of the d series)

	FREE ACIDS $[\alpha]_D^0$	Na SALTS $[\alpha]_D^{20}$	PHENYL-HYDRAZIDES $[\alpha]_D^{20}$	AMIDES $[\alpha]_D$
Gluconic................................	0.0	+11.78	+18.0	+31.2
Mannonic..............................	+15.6	−8.82	−10.5	−17.3
Idonic..................................	+	−2.52	−15.1	−
Gulonic................................	−1.6	+12.68	+13.45	+15.2
Galactonic.............................	−8.0	+0.40	+12.2	+30.0
Talonic................................	?	?	+4.35	−
Allonic................................	−10.0	+4.30	+25.88	−
Altronic...............................	+8.0	−4.05	−15.8	−

TABLE 14

ACIDS	IN 5 PER CENT NaOH $[\alpha]_D^0$		IN 2.5 PER CENT HCl $[\alpha]_D^0$
Chitosaminic.............................	+1.3°	c = 5.0	−15.0°
Epichitosaminic.........................	−5.0°	c = 5.0	+10.0°
Dextro-d-xylo-2-aminohexonic...........	−16.°	c = 2.5	+14.0°
Levo-d-xylo-2-aminohexonic.............	+2 0°	c = 2.5	−11.0°
Chondrosaminic.........................	−15 0°	c = 2.5	−17.0°
Epichondrosaminic....	+1.8°	c = 2.5	+8.0°
Dextro-d-ribo-2-aminohexonic............	+2.0°	c = 2.5	+12 5°
Levo-d-ribo-2-aminohexonic..	−15.0°	c = 2.5	−26.0°

TABLE 15

First group

Chitosaminic acid	Gluconic acid
Chondrosaminic acid	Galactonic acid
d-Levo-xylohexosaminic acid	Gulonic acid
d-Levo-ribohexosaminic acid	Allonic acid

Second group

Epichitosaminic acid	Mannonic acid
Epichondrosaminic acid	Talonic acid
d-Dextro-xylohexosaminic acid	Idonic acid
d-Dextro-ribohexosaminicacid	Altronic acid

divided into two groups as given in table 15.   In the first group, the metallic salts exhibit a higher dextrorotation than the free acids; in the second, the order is reversed.   Thus, accepting as a basis for classification the *sign* of the difference of the molecular rotations of the free acid and of its metallic salt, the contradiction is removed which existed between the conclusions reached on the basis of the properties of the aminohexonic acids and those on the basis of the properties of aminohexoses.

It was shown in the previous sections of this paper that the same rule is applicable for the classification into the d and l series of the simple amino and hydroxy acids as well as of the thio and sulfo acids.   The observations on sugars and amino sugars, and on sugar acids and amino sugar acids, place this rule on a firmer basis.

The practical results of all the investigations in this field of endeavor, then, are the following:

1. All natural amino acids are configurationally related to l-hydroxy acids which, in their turn, are configurationally related to l-tartaric acid.   The amino or hydroxyl groups in these acids have the same allocation as the hydroxyl on carbon atom (2) of mannose.

2. 2-Amino hexoses occurring in nature, chitosamine and chondrosamine, have the configurations of 2-amino glucose and of 2-aminogalactose respectively.

3. In α-amino acids, the deamination by means of nitrous acid takes place without Walden Inversion.

The evolution of these views was very gradual and many schools of thought contributed to it.   Fischer's classical work and the work of Wohl and Freudenberg and Karrer have established by purely chemical methods the configurational relationships between members of the same classes of substances.   Levene and Mikeska have studied the influence on the optical rotation of the polarity of the groups attached to the asymmetric carbon atom.   Frankland and others have studied the influence of structure on optical rotation.   Clough, Karrer, Freudenberg and Levene have made use of these different methods and have added some new ones in order to correlate the configu-

ration of α-amino acids and α-halogen acids with that of α-hydroxy acids and of nitrogenous sugars with simple sugars.

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THE PRECIPITATION LAWS

P. P. VON WEIMARN

I. ON THE NUMERICAL DATA RELATING TO THE LAWS OF PRECIPITATION

The laws governing the precipitation of solid substances from solutions have received a detailed and systematic study in but comparatively recent times.

The law of precipitation according to which the mean magnitude of the individual crystals (subject to the condition that the process of direct crystallization has come to an end, and under exemption from consideration of the stably supersaturated solutions) of precipitates will progressively decrease as the concentration of the reacting solutions progressively increases, was formulated for the first time early in 1906 (2), on the basis of extensive approximately-quantitative investigations with about 60 different salts.

If we plot, along the axis of ordinates, the mean size of the precipitate crystals, and along the axis of abscissas, the concentration of the reacting solutions, we may accept, with a certain degree of approximation, the curves of the general equation: $y \cdot x^n = $ const. (n, being a positive integer or fraction), as the graphical expression of the above precipitation law.

Another law of precipitation, viz.: the law relating to the mean dimensions of the individual crystals prior to the completion of their growth through direct crystallization, was established somewhat later, though also in 1906 (3). This law may be formulated as follows: With progressively increasing concentration of the reacting solutions, the mean magnitude of the individual crystals of precipitates,—as determined after a given time interval, measured from the moment of mixing together the reacting solutions,—will pass through a maximum.

As the time interval selected becomes greater, this maximum is displaced to the left side and upwards.

Such a family of curves, with maxima moving leftwards and upwards, may be expressed analytically by an equation of the form

$$y = k_1 x^{-n} \left(\frac{k_2}{e^{x^n \cdot \tau} - 1} \right)^{-1}$$

where e, is the base of natural logarithms.

Since the precipitation curves with maxima are the first to occur (reckoning from the moment of mixing together the reacting solutions), and since only later (under the above mentioned condition of exempting from consideration the stably supersaturated solutions) do they go over into precipitation curves without maximum, the law given expression to by curveswith a maximum is conveniently called the first law of precipitation, and the law to which the curves without a maximum correspond— the second law of precipitation.

And the third law of precipitation reads as follows: For a set of dispersion media in which a solid substance X has different solubilities, the precipitation curves for that particular dispersion medium in which the solubility is least (assuming all other conditions during precipitation to be nearly—or exactly—the same for the whole set of dispersion media) will occupy the lowest position, beneath all other precipitation curves, and their beginnings will most of all be displaced to the left (4).

As a corollary of the second and the third laws of precipitation, we have the rule (or fourth law of precipitation), which reads as follows: On substituting for the absolute concentration of the reacting solutions (C) the relative concentration of the precipitating substance: $\frac{Q - L}{L}$ (where $Q = \frac{C}{2}$, since we are mixing together equal volumes of the reacting solutions), the precipitation curves without maximum for substance X precipitating from different dispersion media where $L = L_1, L_2, \ldots L_n$, will very closely approach each other, up to the point of sometimes almost merging into a single curve (4).

In view of the fact that some uncertainty prevails in the

literature of dispersoidology in regard to the laws of precipitation, it should first of all be noted that theoretically the precipitation curves will begin—and terminate—with nearly straight lines (5), as shown in scheme A.

The dotted curve, α, corresponds to the instantaneous (for our limited perception powers) formation of the molecules of the
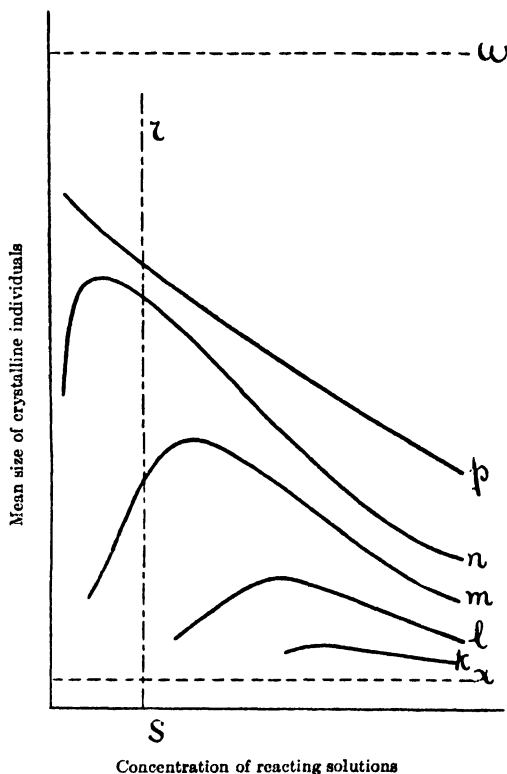
SCHEME A

precipitating substance, or to the sub-ultramicroscopic stage of precipitation (crystallization); the curves: k, l, m, n, p—to finite intervals of time, more and more prolonged, which have elapsed since the moment of mixing the reacting solutions; as regards the curve, ω, since all our measurements are confined to restricted, finite periods of time, and since this curve implies the

recrystallization of all the crystals belonging to each of the precipitates into one single macro-crystal (i.e., visible to the naked eye) for each precipitate, these macrocrystals being, in all precipitates, practically equal in size to one another,—it can never be attained in reality, for it would require, for its realisation, a period of time that would practically be infinitely-protracted.

In actual experiments, we are able to study only those parts of the precipitation curves which lie to the right of the vertical dotted line, rs, since precipitation from slightly supersaturated solutions will often begin only after very extended periods of time.

The whole experimental material so far available, pertaining to the processes of precipitation, includes accurate and complete data for the precipitation of only the five following salts: $BaSO_4$, $CaSO_4 \cdot 2H_2O$ ($CaSO_4$—at elevated temperatures), $SrSO_4$ ($SrSO_4 \cdot 2H_2O$—with high supersaturation, as the less stable phase), Ag_2SO_4, and $AgC_2H_3O_2$, the precipitation having been studied, for all these five salts, from aqueous, as well as from alcoholic-aqueous (ethyl alcohol) dispersion media (6).

The results obtained for the two last-mentioned salts, owing to the absence of any side-phenomena such as, for instance, hydration, formation of aggregate-particles out of the individual crystals, and the like, are especially valuable, being illustrations of the precipitation laws in their pure form, undisguised by any side-influences.

The numerical data for these salts can be duplicated with greater or less approximation, only if all conditions are accurately reproduced.

The study of the precipitation processes of $AgSO_4$ and $AgC_2H_3O_2$ has not been undertaken with the object in view of obtaining any ultra-exact quantitative data, but in order to study, with a degree of accuracy customary for this kind of dispersoidological investigation, the quantitative changes—both in form and in locus, that occur in the precipitation curves under the very same natural conditions under which research-work on dispersoidal synthesis has, so far, been commonly done; that is to say, within

the ordinary range of fluctuations of temperature and pressure in the laboratory.

The variables the influence of which was purposely studied were: concentration of reacting solutions, solubility, and time.

Since the displacement of the precipitation curves is due to direct crystallization only at the very outset of the process (omitting from consideration the very slightly, and consequently— very stably supersaturated solutions), and since later this displacement is produced by the process of recrystallization—i.e., the growth of the larger crystals at the expense of the smaller ones, it is the average magnitude (notably the average length) of the large precipitate crystals[1] that was measured.

In every precipitate we may always distinguish, without difficulty, the especially large individual crystals from the especially small individual crystals. It goes without saying that the especially large individual crystals are not equal to each other; nor are the especially small ones. It is convenient to designate as the category of especially large individual crystals of precipitates, such as do not differ in size by more than 20 per cent; the same may also conveniently be applied to the category of the especially small individual crystals. Evidently, those crystals which belong to neither of the above categories but are of an intermediate size, will constitute the average-size part of the precipitate.

In order to approach, to some extent, the ideal method of studying the precipitation process, this process should be graphically represented as follows (see scheme B).

Two curves of precipitation: one for the especially large individual crystals, and one for the especially small individual crystals should be given. Furthermore, for every experimentally obtained point in the curve, the corresponding content of especially large and especially small crystals should be indicated, in terms of per cent of the whole number of all individual crystals.

Now, in regard to the methods of expressing the mean dimensions of the individual crystals, i.e., whether according to their

[1] Numbers of microphotographs of all precipitates are available, but these have not as yet been analysed.

mean magnitudes as calculated from their weights, or as calcu-
lated from their volumes, the best would be giving separate
precipitation curves for each of the three dimensions: length,
breadth, and depth, together with microphotographs showing the
contours of the individual crystals; without the presentation of
such microphotographs (as will clearly be understood from the
microphotograph (P. 223) of a feathery skeleton-crystal of $BaSO_4$
obtained on mixing up boiling aqueous solutions of 1/10 normal
concentration; magnification—1800-fold), the characterization of
the precipitate, by means of its average linear dimensions, is
far from being complete.

Concentration of reacting solutions
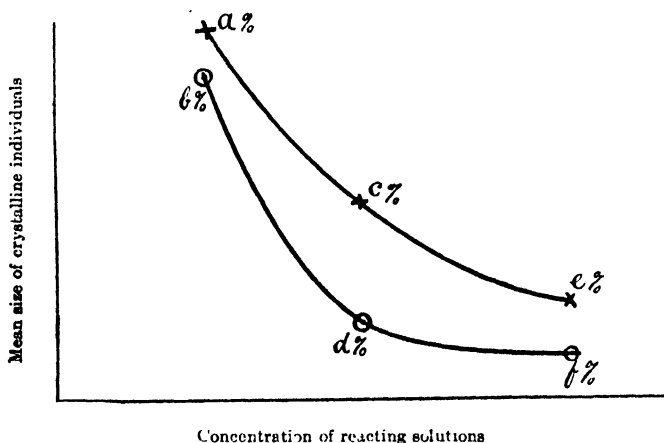
SCHEME B

From the theoretical viewpoint, the best method would be to
use as ordinates of the precipitation curves, the gramme-molecular
surface of the precipitate; or else, the mean dimensions of the
grains in terms of fractions of gramme-molecules.

The preparation of such curves would require, however, a great
deal of meticulous and assiduous work; and so they have never
been met with, so far, in the literature on dispersoids.

Since, in the course of time, the especially small crystals disap-
pear, partially or wholly by solution and reprecipitation in the
form of large crystals it was of particular interest to follow the
process of growth of the especially large crystalline individuals.

For obtaining approximately reproducible results in precipitation it is extremely important always to mix the reacting solutions in exactly the same way; especially with respect to the direction in which the solutions are poured into one another, to the method of stirring applied, and to the volumes mixed.

In the experiments described here the reacting solutions were mixed by rapidly "dumping" the whole amount of one of the reacting solutions into the other, while shaking the vessel with the hand always in the same manner. No mechanical stirring devices have been used.

With respect to the volumes of the reacting solutions, the product: concentration $\times$ volume is kept approximately the same for a given dispersion medium (7).

The solubilities of Ag_2SO_4 at room temperature (20°C.) in the aqueous solutions of ethyl alcohol employed in the experiments were:

gramme-equivalent in 1 litre

In 30 per cent (by volume) ethyl alcohol (average of seven determinations)........................ 0 0106

In 60 per cent (by volume) ethyl alcohol (average of four determinations)........................ 0 00106

Solubility, at 20° of Ag_2SO_4 in water.................. 0 05

The solubility of $AgC_2H_3O_2$ was:

In 50 per cent (by weight) of ethyl alcohol, at 20° (average of two determinations)...................... 0.0088

In water at 20°...................... 0.062

In view of the fact that, in all cases investigated, the lengths of the especially large crystalline individuals have never so diminished, as to fall into the ultramicroscopic domain, the measurement of the separate individual crystals has, in the vast majority of cases, been carried out with an accuracy of 0.001 mm. In most cases, an accuracy of 0.01 mm. is amply sufficient. All experiments were repeated at least two times, the results recorded being the average of all determinations.

II. ON THE NUMERICAL DATA RELATING TO THE VARIABLES REGU-
LATING THE MEAN DIMENSIONS OF THE ULTRAMICROSCOPIC
PARTICLES OF DISPERSE PHASES OF DISPERSOIDAL SOLUTIONS

The mean dimensions of the particles of disperse phases in dispersoidal solutions and in suspensions are, in the general case, determined by two superimposed influences.

The first influence is the one determining the mean dimensions of the individual particles (this is a convenient term for designating the particles that represent individual ultramicrocrystals or individual microcrystals), and the second influence is the one determining the mean dimensions of the aggregate-particles (i.e., loose assemblies of individual ultramicrocrystals or individual microcrystals).

Each of these influences contains a considerable number of variables; this is why one meets with some difficulties in understanding the methods for the determinative regulation of the mean dimensions of particles of disperse phases in both dispersoidal solutions and suspensions.

It is extremely important—both for finding one's way in the confusion that prevails in the literature of dispersoidal synthesis, and also for correctly interpreting the graphs presented here— that it be well understood that the laws of precipitation stated above hold only for individual crystals, not for aggregated particles; and also, that the mean dimensions of the latter are determined by other laws and other variables.

In scheme C, the full lines represent the individual particles, the dotted lines, mixtures of individual and aggregated particles. (The content of the latter class in the disperse phase, *may* amount to 100 per cent.) The horizontal line, MN, is the boundary between the domain of ultramicroscopic dimensions and the domain of microscopic dimensions (larger than $200\mu\mu$).

For substances under conditions, such that their solubility in the dispersion medium is practically nil (e.g.: Au—in pure water; $Al(OH)_3$—in pure water; $BaSO_4$—in 70 per cent ethyl alcohol, etc.), the region of concentrations of the reacting solutions which lies to the left of the vertical line, mn (see scheme C) has, up to the

present time, scarcely ever been studied; because, to the left of line, mn, the concentrations of the reacting solutions are only a small number of times greater than is the saturation-concentration of the precipitate; which substance is practically insoluble.[2]

Concentration of reacting solutions
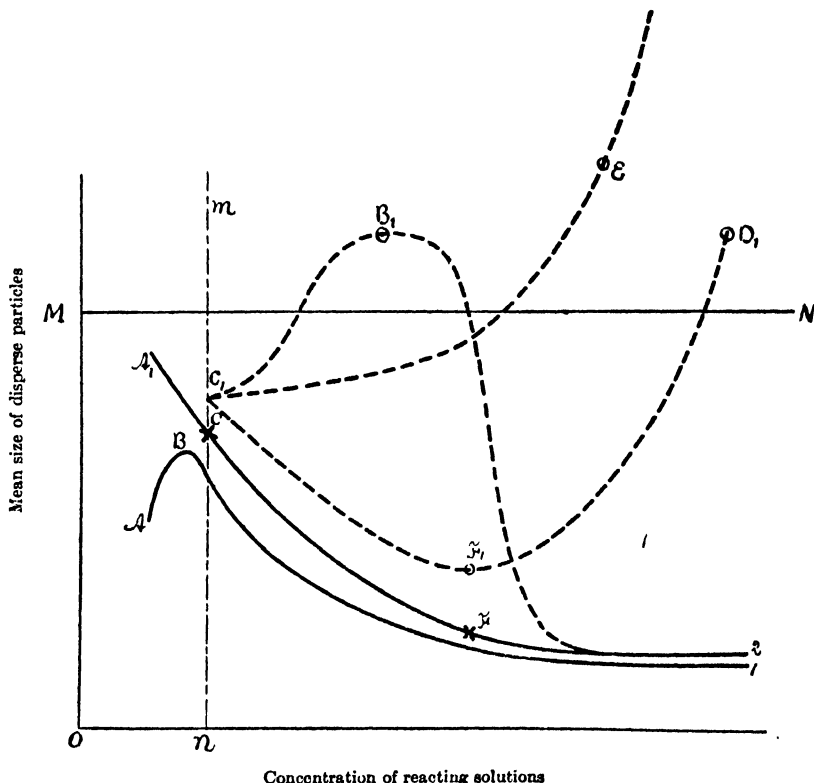
SCHEME C

[2] As regards such cases as $BaSO_4$ in water (solubility—$2,4.10^{-4}$ gramme in 100 cc. water), the precipitation curve similar to the curve AB1 can actually be realized over its greater part; but, in the course of time, it will soon go over into a curve similar to A_1CF_2, except that, in its upper (left-hand) part, it will stretch out considerably beyond the boundary of the ultramicroscopic domain; we thus see that, in the present instance, the dispersoidal solutions will very rapidly turn into instable suspensions of microcrystals-individuals, on account of the rapid growth of the ultramicrocrystals.

In the case of the most typical dispersoidal solutions only the region to the right of the line, mn, say, beginning with the point C has been investigated.

Only when no powerful aggregators are formed as by-products of the reaction, or when, dispergators are formed, or introduced, may the line CF2 exist, over some definite interval of concentrations, for a sufficiently long time to make observations and in proportion as the aggregation of the individual ultramicrocrystals occurs, the curve CF2 will assume, after the lapse of a certain time, the position of the curve $C_1F_1D_1$.

It is quite obvious that, in the above case, over the range of concentrations between the points C_1, F_1 (respectively, C, F), the curve C_1F_1 (for a mixture of individual and aggregated particles) will portray the same mutual dependence between the mean dimensions of the particles of disperse phase and the concentration of the reacting solutions, as that expressed by the second law of precipitation, i.e., with increasing concentration of the reacting solutions, the mean dimension of the disperse particles will decrease.

In the above case, the aggregation has not yet gone so far as to mask the second law of precipitation.

If, however, the by-products of the reaction happen to be powerful aggregators, the precipitation curve will assume the form C_1E,—provided that the large microscopic and macroscopic flakes are aggregate-particles.

Since it is only the small aggregate-particles that are likely to be mistaken for individual ones, the large aggregate-flakes being easily recognized as possessing a very delicate grainy structure, the form C_1B_12, has been sometimes attributed to the precipitation curve under the erroneous impression that this curve was an example of the first law of precipitation for the individual crystals (8).

If any complicated aggregation (coagulation) processes are at play (see the curves illustrating the effect of electrolytes on the duration of life of the dispersoidal solutions (figs. 14 to 24) the precipitation curves which express the interdependence—not between the average size of the individual crystals and the con-

centration of the reacting solutions, but between this latter and the average size of particles in a mixture of individual and aggregated disperse particles—may also exhibit a more complicated form than that exhibited by the three (dotted) curves of scheme C.

The second misapprehension which is frequently met with in the literature devoted to dispersoidal synthesis consists in the erroneous method employed for expressing the concentration of the actual reacting molecules in the solutions used.

Thus, for example, in the case of (a) the preparation of dispersoidal solutions by means of hydrolysis of (b) the splitting up, with water or alcohol, of double salts of the type: $AgNO_3 \cdot AgX$; $AgX \cdot KJ$,—where X = a halogen and (c) in some measure, also of the reduction of Au by the formol-method, and many other instances, the principal reacting molecules are obviously the molecules of water, and it is by the ratio of their number to the number of the hydrolysing salt molecules that the velocity, as well as the degree of completeness, of the hydrolytic process is determined; it is quite plain that, in the cases now under discussion, the active mass of water is in inverse ratio to the concentration of the salts in the solutions used for the experiments.

Hence, the results obtained in dispersoidal synthesis by the method of hydrolysis—of $Fe(OH)_3$, $Al(OH)_3$, and so on—are not contradictory to, but rather confirm the general laws of precipitation. In the cases under consideration the precipitation curves will be of the types CF2 and $C_1F_1D_1$ (9), if the reciprocal of the concentration is plotted along the axis of abscissas.

Of all the cases of dispersoidal synthesis that up to now have been thoroughly studied quantitatively, the case which is the most easily reproducible (10) is the dispersoidal synthesis of selenium, by the method of pouring weak solutions of it in aniline or quinoline, into ethyl alcohol (93.5 to 90 per cent—by weight).

These dispersoidal solutions have moreover received the most thorough study, in connection with the effects produced on the mean magnitude of the disperse particles by the different variables.

This is the reason why the numerical data relating to this system have been selected for presentation here.

In order to facilitate the analysis of the dispersoidal synthesis, the coefficient expressed by the following formula (11):

$$\delta = J \frac{Q - L}{L}.$$

is convenient. $Q - L$, is the concentration of the disperse phase produced; L, the ordinary solubility (i.e., the solubility of the large crystals) of the disperse phase, and J, the product of all other variables influencing the mean magnitude of the individual ultramicrocrystals, each of these variables being expressed in abstract numbers equivalent to that of the ratio $\frac{Q - L}{L}$.

For instance, if the viscosity of the dispersion medium is increasing, J will also increase; or if, independent of the variable L, the rate of the decrease of the concentration, from the value Q, down to the value L, is increasing, J will also increase; etc.

Since only very low concentrations of the selenium solutions are used, and since no powerful aggregators arise in the dispersion medium, it so happens that the fundamental precipitation laws for the individual ultramicrocrystals (though having undergone slight quantitative alterations due to aggregate-particle formation), remain unaltered in their essence.

The graphs for these systems are very explicit in showing that, with the increase of the dispersion coefficient δ, whatever the means by which this increase may have been produced, the mean magnitude of the particles of the disperse phase in the dispersoidal solutions and the suspensions of selenium, will decrease.

III. ON THE NUMERICAL DATA RELATING TO THE PROCESSES OF DISPERGATION OF THE PRECIPITATES IN STATU NASCENDI

Although the phenomena of dispergation of precipitates have been frequently investigated (12) (13), both as regards their exactitude (in comparison with other data) and their comprehensiveness, the best illustrative data are those obtained in studying the dispergation of $BaSO_4$ precipitates in statu nascendi, in 63 per cent. (by weight) ethyl alcohol.

Check experiments were carried out at room temperatures, the results obtained being practically identical.

IV. ON THE NUMERICAL DATA RELATING TO THE DEPENDENCE OF
THE AMOUNT OF ADSORPTION ON THE SOLUBILITY, OF A GIVEN
SALT FOR DISPERSION MEDIA IN WHICH THE SALT HAS DIF-
FERENT SOLUBILITIES

The numerical data illustrating the dependence between the solubilities of a given substance in different dispersion media, and the amount of adsorption of that substance, by a definite adsorbent, out of these media, are extremely scanty (14).

The only existing data for salts are displayed graphically below.

As adsorbent, BaSO₄ (Merck's extra pure, for x-ray diagnosis); in amounts of 20 grammes per 100 cc. of the solution of the salt to be studied, was employed. The salt solution was shaken, with a BaSO₄ precipitate, for ten minutes, after which the precipitate was allowed quietly to settle during twenty-four hours. The clear supernatant solution was then analysed.

Such was the procedure in studying the adsorption by BaSO₄ precipitates of all salts, except BaCl₂ from alcoholic-aqueous solutions. In these solutions the BaSO₄ became partially dispergated, under the influence of the BaCl₂ molecules, into suspensions (respectively—into dispersoidal solutions, in part) that took a long time to clear up completely.

These solutions were therefore centrifuged, in order to obtain a clear solution for analysis.

In table 1 below are given the concentrations of the salt solutions used for the experiments.

The concentrations of the salt solutions before and after adsorption (i.e., the initial and the resulting concentrations) were always determined by exact analytical methods; in the cases of the solutions of Al₂(SO₄)₃, Na₂SO₄, K₂SO₄, NiSO₄ and CoSO₄, the amount of sulphate ion was determined gravimetrically as BaSO₄; in the case of the MnSO₄, Mn was determined as pyrophosphate; and in the cases of CuCl₂ and CuSO₄, Cu was determined by the very exact method of De-Haën-Low (iodometry); in the case of BaCl₂ the Ba-ion was determined as BaSO₄.

TABLE 1

CONCENTRATIONS OF SALT SOLUTIONS IN GRAM-MOLECULES PER LITER

DISPERSION MEDIA	$Al_2(SO_4)_3$	Na_2SO_4	K_2SO_4	$MnSO_4$	$NiSO_4$	$CoSO_4$	$CuSO_4$	$CuCl_2$	$BaCl_2$
Pure water	$1.0297 \cdot 10^{-2}$	$1.3918 \cdot 10^{-2}$	$0.9898 \cdot 10^{-2}$	$0.9959 \cdot 10^{-2}$	$1.0925 \cdot 10^{-2}$	$1.1178 \cdot 10^{-2}$	$0.9797 \cdot 10^{-2}$	$0.9756 \cdot 10^{-2}$	$0.9884 \cdot 10^{-2}$
10 per cent ethyl alcohol	$1.0364 \cdot 10^{-2}$	$1.3807 \cdot 10^{-2}$	$1.0597 \cdot 10^{-2}$	$1.0016 \cdot 10^{-2}$	$1.0478 \cdot 10^{-2}$	$1.0546 \cdot 10^{-2}$	$0.9731 \cdot 10^{-2}$	$0.9728 \cdot 10^{-2}$	$0.9937 \cdot 10^{-2}$
20 per cent ethyl alcohol	$1.0314 \cdot 10^{-2}$	$1.3902 \cdot 10^{-2}$	$1.0064 \cdot 10^{-2}$	$0.9833 \cdot 10^{-2}$	$1.0844 \cdot 10^{-2}$	$1.0575 \cdot 10^{-2}$	$0.9741 \cdot 10^{-2}$	$0.9731 \cdot 10^{-2}$	$1.0106 \cdot 10^{-2}$
40 per cent ethyl alcohol	$1.0229 \cdot 10^{-2}$	$1.3743 \cdot 10^{-2}$	$0.9932 \cdot 10^{-2}$	$0.9774 \cdot 10^{-2}$	$1.0585 \cdot 10^{-2}$	$1.0475 \cdot 10^{-2}$	$0.9722 \cdot 10^{-2}$	$0.9678 \cdot 10^{-2}$	$1.0029 \cdot 10^{-2}$

In all the above cases of studying adsorption, the experiments were repeated two or three times, and the results recorded were the average results.

V. ON THE NUMERICAL DATA RELATING TO THE INFLUENCE ON THE DURATION OF LIFE OF DISPERSOIDAL SOLUTIONS, OF A PROGRESSIVE INCREASE OF THE CONCENTRATION OF ELECTROLYTES IN THE DISPERSION MEDIUM.

In spite of the fact that indications are not unfrequently met with in the literature on dispersoidology, to the effect that some dispersoidal solution or other has an "unlimited" stability, it is to be maintained that the life of every dispersoidal solution of any practically insoluble substance, is limited in time.

This should be noted first.

Second: the duration of life of dispersoidal solutions is determined by a very large number of variables among which the electrical conditions are by no means always the predominant. In fact, the influence of the electrolytes themselves is the resultant of quite a number of processes and consequently is far from being always so simple as sometimes represented (15).

Especially in those cases when the relative concentration of the disperse phase $\left(\dfrac{Q - L}{L} \right)$ is not large, the number of variables controlling the life of such kinds of dispersoidal solutions will so increase, that the phenomena will sometimes begin to acquire an accidental character.

Such cases, however, have so far received but very little study, and usually the relative concentration $\dfrac{Q - L}{L}$ of the dispersoidal solutions is expressed by very large numbers.[3]

Up to the present time, the influence of the electrolytes on the duration of life of dispersoidal solutions has, for the most part, been studied in instances of dispersoidal solutions resulting from chemical reactions.

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[3] For instance, if the concentration of the dispersoidal solution is equal to 1.10^{-2} gramme, and the true solubility of the substance—to 1.10^{-12} gramme, $\dfrac{Q-L}{L}$ will come to about 10,000,000,000.

But, under the above conditions, the different kinds of admixtures present in the dispersion medium would render the study of the influence exerted by the electrolytes extremely complicated, and the numerical data, difficultly reproducible.

In one isolated case, it is true, the effect of electrolytes (16) on a dispersoidal solution of sulphur prepared by a physico-chemical method (pouring alcoholic-aqueous sulphur solutions into water (17)) has been studied, but then only in the sense of determining the "Coagulating-Concentration" of the electrolytes.

Complete "Life-curves" of dispersoidal solutions, i.e., curves with the coördinates: concentration of electrolyte, duration of life, have but recently been realized, for the case of a dispersoidal solution of sulphur, prepared by the mechanical method of pulverizing sulphur together with grape-sugar.

Unfortunately, for "positive" dispersoids, the only part of the "Life-curves" that has so far been realized is their right-hand, descending branch; and this notably for dispersoidal solutions of the hydroxide of aluminium, prepared by the same mechanical method as mentioned for the case of dispersoidal solutions of sulphur.

The numerical data relating to the above disperse systems are presented graphically.

The dispersoidal solutions of sulphur were prepared as follows: 0.1 gramme of purest rhombic sulphur, specially recrystallized, was treated by grinding, for one hour, in an agate mortar, together with 0.9 gramme of grape-sugar (Merck's anhydrous, extra-pure); of the resulting mixture, 0.2 to 0.3 gramme were taken, and ground again, in small portions, in an agate mortar, for two hours more; from this last grinding, 0.15 gramme was taken, and quickly introduced, under vigorous stirring, into exactly 100 cc. of specially purified, freshly re-distilled (using a silver condenser) water.

The disperse systems of sulphur prepared in the above described manner were then filtered off from the coarsely-disperse .parts, through a filter (S. and S. No. 602, "extra-hart").

The resulting dispersoidal solutions of sulphur prepared at different times after the manner described above (at temperatures

between 30° to 20°C.; in the summer months), were of a concentration between 30 to 20 mg. sulphur per litre, and of an average size of particles between 90 to $80\mu\mu$.

The duration of life was expressed in terms of days (1 day = 24 hours) elapsed from the moment of preparation of any given dispersoidal solution, up to the moment when the sedimentation of the whole of the disperse particles present was practically completed. In the case of the dispersoidal solutions of sulphur now under consideration, this latter occurrence is easily recognized from the complete disappearance of opalescence which, in the cases under consideration, exactly coincides with the practically complete disappearance of any Tyndall cone produced by the rays of an arc lamp, whenever the experiments are carried out in a dark room. The temperature varied during the experiments, between 30° and 20° (in the summer months). In the winter months (at temperatures fluctuating between 10° to 4°) the dispersoidal solutions of sulphur had a considerably greater stability.

The preparation, by the mechanical method, of dispersoidal solutions of aluminium hydroxide was done in exactly the same manner as in the case of sulphur, except that, of the material resulting from the last grinding, 0.3 gramme were introduced into 200 cc. of water. The alumina used was composed of microcrystals of $Al_2O_3 \cdot 3H_2O$ (obtained by the method Shulten-Weimarn from a dilute solution of $Al(OH)_3$ in strong aqueous NH_4OH). Since a positive dispersoid was desired filtration could not be used; and consequently after settling, the supernatant liquid was pipetted off and used for the experiments. The concentration of the dispersoidal solutions employed varied between 50 to 60 mg. of $Al_2O_3 \cdot 3H_2O$ per litre of the solution, and the average size of the disperse particles was 85 to $95\mu\mu$. The dispersoidal solutions of aluminium hydroxide contained particles of a variety of different dimensions as evident from the initial rapid sedimentation of the coarser particles.

The duration of life was measured in terms of days (1 day = 24 hours), from the moment of preparation of the dispersoidal solution, up to the complete disappearance of any Tyndall cone.

The temperature during the experiments was varying between 10° to 4° (winter months).

The duration of life of the dispersoidal solutions of aluminium hydroxide without the addition of electrolytes amounts to a few (e.g., 2 to 3) months; and therefore, the left-hand parts of the "Life-curves" have not yet been determined.[4]

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EXPLANATION OF FIGURES

(1) The dispersion medium is indicated thus (93% C_2H_5OH); *(2)* The direction of pouring is indicated by the arrow. *(3)* The time, t_o, represents the period (*ca.* 10- 15 min.) required for the operations of sampling and photomicrographing. *(4)* All data shown are the average of at least two independent experiments.

1. *Precipitation of Ag_2SO_4.*—Reaction: $AgNO_3$ + $MnSO_4$ = Ag_2SO_4 + $Mn(NO_3)_2$. Figs. 1-7, incl. Per liter of final solution, C = Ag_2SO_4 produced by the reaction and S = its solubility, both in g-equivalents.

2. *Precipitation of $AgC_2H_3O_2$.*—Reaction: $AgNO_3$ + $KC_2H_3O_2$ = $AgC_2H_3O_2$ + KNO_3. Figs. 8-9.

3. *Precipitation of Se.*—Reaction: (a) 5 cc. of aniline containing m milligrams of Se are poured into 100 cc. of 93.5 wt. % C_2H_5OH; or (Fig. 13) mixtures thereof with An. or glycerol. t = 20°. Figs. 10-13, *a*-curves.

(b) As in (a) but with quinoline instead of aniline and using 90 wt. % C_2H_5OH. Figs. 10-13, *b*-curves.

4. *Effects of salts dissolved in the dispersion medium.*—Reaction: (a) $BaSO_4$.—50 cc. (= $2a$ + $2x$ equiv.) BaH_2 + 50 cc. (=$2a$ equiv.) $MnSO_4$ = a equiv. $BaSO_4$ + a equiv. MnR_2 + x equiv. BaR_2. Dispersion medium, 63 wt. % C_2H_5OH. Figs. 14-17.

(b) S.—Dispersoidal solutions of sulphur prepared by the method of grinding with sugar. *Ca.* 25 milligrams S per liter of H_2O; particles *ca* 85 $\mu\mu$. Figs. 18-28. C = millimols salt per liter. The dotted horizontal is for C = 0. To the right of the dotted vertical (fig. 23) the disperse phase begins to dissolve by chemical action.

(c) Al $(OH)_3$.—Prepared as in (b) *supra*. *Ca.* 55 milligrams $Al_2O_3 \cdot 3H_2O$ per liter of H_2O; particles *ca.* 90 $\mu\mu$. Fig. 24. The dotted horizontal is for C = 0. Dissolving begins at points marked with crosses.

5. *Adsorption and Solubility of Salts.*—Fig. 25.

Fig. 2
(30 Vol %C₂H₅OH) Mn — ▸ Ag

Fig. 3
(60 Vol %C₂H₅OH) Mn ⟶ Ag

Fig. 1   (H₂O) Mn ⟶ Ag

Fig. 6
(H₂O)
Mn ⟶ Ag
Ag ⟶ Mn

Fig. 7
(30 % C₂H₅OH)
Mn ⟶ Ag
Ag ⟶ Mn

Fig. 4

Fig. 5
o ~(H₂O) t₀ +6 months
• ~(30 % C₂H₅OH) t₀ +6 months
□ ~(60 % C₂H₅OH) t₀ +1 month

Fig. 9

(50 wt% C₂H₅OH)

K ⟶ Ag

Average length (mm) of crystals

Conc. of reacting solns, g-equiv per l

Fig. 8

(H₂O)

K ⟶ Ag

t₀ + 13 days

t₀ + 1 hour

t₀ + 10 min.

t₀

Average length (mm) of crystals

Conc. of reacting solns., g-equiv per l

Fig. 10

a Interpolated
▲ Experimental

Average diam. (μμ) of particles at room temp.

Temp. of alc. solns. at moment of mixing

Fig. 11

○ Experimental
▲ Interpolated

Average diam. (μμ) of particles at room temp.

+60°
+30°
+25°
0°
−30°
−60°
−90°

238

Fig. 12

Fig. 13

Fig. 14

Fig 15

Fig. 16

Mn SO₄ ⟶ BaCl₂

Fig. 17

Mn SO₄ ⟶ Ba NO₃)₂

Fig. 18

+ BaJ₂
□ NaCl
△ BaCl₂
× CaCl₂
○ CeCl₃

Fig. 19

Fig. 20

Fig. 21

Fig. 22

Fig. 23

Fig. 24

Fig. 25

BIOCHEMISTRY OF THE FATS

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By the Biochemistry of Fats is meant the chemistry of the fats in their relation to living organisms.[1] It involves, therefore, not only the fatty acid tri-esters of glycerol which are the fats proper, but other compounds of the fatty acids which are associated with them in the life processes of living things.   On this basis consideration must be given to such substances as the lecithins and cephalins, and a number of others in which the central figure is the fatty acid.   In recognition of their relationship a classification of these substances was presented some years ago by Gies and Rosenbloom (1), and adapted with slight modifications by Mathews in his text book (2).   The classification included a number of substances, such as the essential oils and fat colors, which are not concerned in any way with the biochemical relations of the fats, and besides seemed unnecessarily complicated.   A somewhat simpler classification based more strictly on the relationships of the various substances to the fats was later proposed (3), and is given in a modified form below. Three terms have been suggested for the group, namely, "Lipins"

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[1] Reviewer's note: In writing this review attention has been confined largely to those phases of the subject which are of definite interest to the student of life processes of living things.   Many substances and reactions that are of mainly chemical or technical interest have, for this reason, been omitted or dealt with briefly.   For reasons of space, other topics which have been reviewed adequately elsewhere within a brief period have been passed over lightly.

The literature on this subject has grown to be enormous and it was felt that little would be gained by reference to all the articles on a given topic.   Consequently only those which in the reviewer's opinion are of outstanding importance in the discussion are quoted but care has been taken to include those which contain full references so that the reader who wishes more detailed information may know where to find it.

by Gies and Rosenbloom, "Lipides" by the International Congress of Applied Chemistry, and the old term "Lipoids" by the author. The term lipins has been used in a different sense by Leathes, and was later adopted by McLean in his monograph as a name for a subgroup containing the cerebrosides and the phosphatides. The term lipoids is understood by many to exclude the fats, although used in the wider sense by many workers on the continent. For these reasons, and for the sake of uniformity, the author recommends the use of the term Lipides as the general group name. The modified classification is as follows:

Lipides

Substances having the following characteristics:
  a. Insolubility in water and solubility in the fat solvents, such as ether, chloroform, benzene.
  b. Relationship to the fatty acids as esters, either actual or potential.
  c. Utilization by living organisms.
Simple lipides. Esters of the fatty acids with various alcohols.
  Fats—esters of the fatty acids with glycerol.
  Waxes—esters of the fatty acids with alcohols other than glycerol.
Compound lipides. Esters of the fatty acids containing groups in addition to an alcohol and fatty acid.
  Phospholipides—substituted fats containing phosphoric acid and nitrogen—lecithin, cephalin, spingomyelin.
  Glycolipides—compounds of the fatty acids with a carbohydrate and containing nitrogen but no phosphoric acid—cerebrosides.
  Aminolipides, sulfolipides, etc.—groups which are at present not sufficiently well characterized for classification.
Derived lipides. Substances derived from the above groups by hydrolysis.
  Fatty acids of various series.
  Sterols—mostly large molecular alcohols, found in nature combined with the fatty acids and which are soluble in the fat solvents—cholesterol ($C_{27}H_{43}OH$), myricil alcohol ($C_{30}H_{61}OH$), cetyl alcohol ($C_{16}H_{33}OH$), etc.

Almost all the known lipides are found in living organisms, so that the general characteristics of the group are in the main those of naturally occurring substances. But such substances as have been produced synthetically behave, as far as is known, like the natural ones, and there is no reason to believe that the characteristics of the group will have to be altered to suit synthetic members. Thus this classification which was intended for biochemical purposes answers very well in the wider sense as a chemical classification.

The most general characteristic of the group is the solubility in fat solvents such as ether, chloroform, benzene, as contrasted with the insolubility in water. This of itself is sufficient to set it off from the other great groups of biological substances— the carbohydrates, proteins, and mineral salts. The property is not absolute, since certain members of the group such as the lecithins form dispersons on mixing with water, which are at least colloidal and may approach true solubility. On the other hand, many members of the group are not soluble in all fat solvents. For example, most of the lecithins are insoluble in acetone, the cephalins are mainly insoluble in alcohol, while sphingomyelin and the cerebrosides are difficulty soluble in ether.

In order to exclude organic compounds which have no biochemical relationship to the fats or fatty acids, but which from their solubilities alone would be included in the group the limitations in (b) and (c) have been applied. The substances included in the group must be either ester-like combinations of the fatty acids or capable of forming such combinations, and they must be capable of performing some useful functions in living organisms.

THE SIMPLE LIPIDES

Fats

Esters of the fatty acids with glycerol. These are commonly called oils when they remain liquid at ordinary temperatures, and fats when solid. They are the most important of the

lipoids from the point of view of quantity, wideness of distribution, food value, and commercial interest. They constitute the main form of food storage in animals, and share with carbohydrates and to a less extent with proteins this function in plants. As they occur naturally they are always mixtures of triglycerides of various fatty acids, and their properties vary with the nature of the fatty acids in the separate glycerides, and with the nature of the glycerides composing the mixture.

The glycerides of the higher fatty acids are insoluble in water, those of the lower fatty acids, e.g., butyric, are slightly soluble. In the organic solvents such as ether, chloroform, benzene, all are readily soluble even in the cold and much more soluble hot. In ethyl and methyl alcohol and acetone they are slightly soluble in the cold but readily soluble when hot. In fact boiling ethyl alcohol is one of the best solvents for use in extracting tissues, giving a cleaner extraction than ether, chloroform or benzene, probably because, owing to its affinity for water, it penetrates the tissue better. The solubility in alcohol, like the melting point, varies with the nature of the combined fatty acid, the glycerides of the unsaturated and the lower fatty acids being more soluble than those of the higher and saturated acids. The glycerides of the hydroxy fatty acids like the acids themselves are insoluble in petroleum ether.

Melting point and solidifying point. In general the melting points of the glycerides are higher than those of the contained fatty acids and vary with the fatty acids, the glycerides of the higher saturated acids having the highest melting points, those of the lower fatty acids lower, and those of the unsaturated acids still lower. The melting point of a natural fat, which is always a mixture of glycerides, depends on the nature of the component glycerides. Its melting point may be low because it contains either glycerides of the lower acids or glycerides of the unsaturated acids. The melting points of mixtures of pure glycerides cannot be foretold from the melting points of the constituents. Eutectic mixtures are formed of which the melting points pass through a characteristic minimum value below that of either of the constituents. On the other hand, having

determined the curve of melting points of various known mixtures of pure triglycerides it is possible to determine the composition of an unknown mixture with a fair degree of accuracy, a fact which has been made use of by Twitchell (4).

The solidifying point of a glyceride or mixture of glycerides is always lower than the melting point, the difference being generally considerable and often wide. Thus the melting point of tristearin is given as 71.5°, its solidifying point 52.5° (Lewkowitsch). A sample of beef fat (from the heart) melted at 49.5° and solidified at 36° (5). Butter fat melted at 34.5° and solidified at 22.7°. (Stearic acid melts and solidifies at practically the same temperature (69.3°).) Analogous to these findings is the fact that pure triglycerides under certain conditions will exhibit a double melting point. Tristearin, for example, which had just been melted will melt at 55° then on raising the temperature it will solidify and melt again at 71.5° (6). The above peculiarities of the glycerides conflict with the physical law that phenomena of this nature should take place at the same temperature, and a considerable amount of work has been done to clear up the inconsistency. Thus it was found by Guth (6) and Le Chatelier and Cavaigac (7) that well crystallized tristearin has but one melting point (71.5°). If however, it was examined shortly after having been melted it showed two melting points due to a delayed cooling. A similar conclusion was reached by Le Chatelier and Cavaigac (7) who showed that in glyceride mixtures the change from liquid to solid is extremely slow, and that if the observations be carried out with sufficient slowness the melting and solidifying process reverses within 0.1 to 0.2 degrees. Brigl and Fuchs (8) claimed that fatty acids of identical structure may differ in their melting point depending on the different orientation of the carbon atoms in the crystal—the existence of two forms of the same acid which may change into each other. Bömer (9) found that tristearin obtained by crystallization from ether melted at 71.6° to 72.2° and solidified at 70°. If, however, the crystals were heated above this melting point a few degrees they solidify at 52°, and exhibit the double melting point at 55° and 71.6°.

Grün and Schacht (10) prepared synthetically three mixed glycerides which could be prepared in either the lower (labile) or higher (stable) melting forms. The labile form could be gradually converted into the stable by seeding with a crystal of the stable form, but the reverse change was not possible. The results of these workers seem to indicate that some unknown factor comes into play, possibly the existence as suggested, of two forms of the glycerides, although from our present knowledge of the structure of the glycerides it is difficult to see how such forms could be explained. From a practical point of view the rule has originated that to get a true melting point it is necessary for the fat to stand for at least twenty-four hours in the melting point tube before the determination is made.

The delayed solidification appears to be of considerable importance in the living animal since many stored fats have a melting point considerably above body temperature, while the solidifying point is some degrees below [note beef fat above].[2]

Color, odor, etc. The pure triglycerides are colorless, odorless and tasteless, the properties of color, odor and taste when present being due entirely to foreign substances mixed with or dissolved in them. Thus the desirable yellow color of butter is due to plant pigments carried over from the food. Plant pigment is also responsible for most of the color of the stored fat of animals (12) (13). The flavor of food fats is also due to foreign materials absorbed by the fat, either from its natural environment, or formed during the processes of preparation. In modern butter making the bacterial flora is carefully controlled with this point in mind.

Glycerides. The glycerides composing the natural fats may be either simple, containing only one fatty acid, or mixed, containing more than one acid, and, far from being rare constituents of the natural fats as was first believed, more recent investigations tend to show that mixed glycerides form the bulk of many of the natural fats. They have been prepared syn-

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[2] A condition has been noted in infants (Sclerema neonatorum) in which the subcutaneous fat has hardened resulting in the death of the infant (11). In this case the abnormality found was a high content of free fatty acid.

thetically in large numbers. The methods of synthesis are not markedly different from those for the simple glycerides, but the procedure is somewhat complicated by the fact that there is more or less shifting of the radicles in the molecule. For example Kreis and Hafner (14) found that when oleic acid was allowed to act on di-palmitin and di-stearin considerable quantities of tri-palmitin and tri-stearin were found, while the yields of oleodi-palmitin and -stearin were correspondingly reduced. It should be noted that the phospholipides, lecithin and cephalin, are naturally occurring mixed triglycerides, containing two different fatty acid radicles and one phosphoric acid radicle.

Optical properties. Certain of the mixed triglycerides should be optically active, since they contain an asymetric carbon atom. Thus:

$$C_3H_5 \diagdown \begin{matrix} O.R_1 \\ O.R_2 \\ O.R_3 \end{matrix}, \quad C_3H_5 \diagdown \begin{matrix} O.R_1 \\ O.R_1 \\ O.R_2 \end{matrix}, \text{ should be optically active}$$
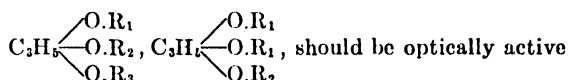
as a matter of fact the only optically active fats which are found in nature are those which contain optically active fatty acids as, for example, castor oil and chaulmoogra oil, and those which contain optically active non-fat substances such as resins, sterols (cholesterol, phytosterol, etc.). Unsuccessful attempts have been made from time to time to prepare optically active glycerides (15) (16).

Hydrolysis (saponification). Fats are hydrolyzed in the laboratory in the same way and with the same agents as are simple esters. Water at high temperature (under pressure) as in the autoclave may be used either alone, or more advantageously with catalysts such as acids or alkalis. At ordinary pressures the same catalysts do the work, but more slowly. The speed of reaction may be increased by the use of a solvent, such as alcohol, which dissolves the fats. Amyl alcohol is more effective than ethyl alcohol, probably because of the higher temperature which can be obtained.

Enzyme hydrolysis is effective when the fats are emulsified. Fat-splitting enzymes or lipases are present in the gastro-in-

testinal secretions of animals, and in many plants especially in fatty seeds as the castor bean, seeds of chelidonin majus, the rubber plant, etc.

Synthesis. Synthesis of the glycerides is carried out along the same lines as synthesis of the simple esters, but is complicated by the fact that glycerol is a triatomic alcohol with two different positions, and by the fact that there may be shifting of the groups from one position to the other. The special problems involved are reviewed by Amberger and Bromig (17), and the question of optical activity of the glycerides by Bergmann and Sabetay (16) and Abderhalden (15).

Synthesis of fats by enzymes has been successfully demonstrated with castor bean lipase by Welter (18), and Armstrong and Gosney (19), who gave a beautiful demonstration of the reversibility of the synthetic-hydrolytic powers of the castor bean lipase. Synthesis by lipase of the pancreatic juice has been demonstrated by Hamsik (20), Taylor (21) and Foá (22).

Rancidity. Dry air, excluding moisture and light, has apparently no effect on oils and fats. Air in presence of moisture and particularly of light and heat rapidly brings about those changes known collectively as rancidity. Unsaturated fats become rancid more quickly than saturated, and free fatty acid formation appears to be the first essential for rancidity. The stages in the process have been outlined by Kerr and Sorber as follows (23). First the development of free acid, then a drop in free acid coincident with the rancidity, followed again by increased acidity. The iodine value falls, unsaponifiable matter increases, and oxygen is fixed in peroxide form of the following nature

$$CH_3 \cdot (CH_2)_7 \cdot CH \underset{\underset{O \longrightarrow O}{|\qquad\;|}}{\longrightarrow} CH \cdot (CH_2)_7 \, COOH$$
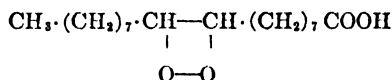
This substance then acts as a carrier of oxygen for the production of various oxidation compounds, the nature of which is unknown. Greenbank and Holm (24) found that metals catalyze powerfully the production of rancidity.

Waxes—esters of the fatty acids with alcohols other than glycerol

Waxes are very widely distributed in the plant and animal kingdom, their main usefulness being apparently as protective agents due to their chemical inertness. Thus, the high lipide content of the tubercle bacillus is due mainly to the waxes and wax alcohols in contains. Insect waxes and leaf waxes are esters of higher alcohols and mainly higher saturated acids. Thus the main constituent of beeswax is myricyl palmitate.

A group of waxes which is of particular importance to the biochemist is that of the esters of cholesterol and related alcohols with various fatty acids. In animals these occur in largest amount in blood plasma. Similar esters may occur in plant tissues, but so far, no mention has been made of them. The cholesterol esters of blood plasma have been found to consist mainly of esters of palmitic, oleic and linolic acids with smaller amounts of stearic and other acids. In addition to the blood plasma the esters are to be found in large amounts only in the suprarenal glands. Small amounts occur in the liver, kidney, heart, and probably in other organs and tissues, but the quantities are generally so small that there is always a question whether they are real constituents of the tissues or are due to the blood plasma present. In some abnormal conditions, such as amyloid kidney, undoubted deposits of esters occur. The waxes are considerably more difficult to hydrolyze than the fats, and this difference has been made use of in separating them, in particular cholesterol esters, from the fats (25). For complete saponification of the cholesterol esters special means must be employed, for instance, the use of sodium ethylate on the esters in ethereal solution (26).

COMPOUND LIPIDES

Phospholipides

We are indebted largely to MacLean in England and to Levene in this country for clearing up this previously very complicated subject, and reducing the large number of poorly determined and doubtful compounds to a few which they have been mainly

instrumental in defining. The best characterized members of the group are the lecithins, cephalins, and sphingomyelin.

Sphingomyelin. Composition. The substance as prepared contains two fatty acid radicles, one probably lignoceric acid, and about an equal amount of a low melting acid, probably a hydroxy acid, two bases—sphingosine and neurine or choline, and phosphoric acid. Sphingomyelin apparently contains no unsaturated acid.

A formula suggested by Levene (27) is as follows:

$$\underset{\text{choline}}{O=P{\overset{\displaystyle\overset{\text{\textit{sphingosine}}}{O}-C_{17}H_{32}(OH)NH}{\underset{\displaystyle O.C_5H_{13}N(OH)}{-OH}}}}$$
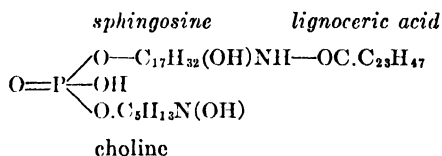
Properties. It is a relatively stable substance, undergoing no change in air or light, is soluble in hot alcohol from which it separates on cooling in crystalline form, relatively insoluble in cold or hot ether, easily soluble in cold or hot chloroform, benzene, pyridine and glacial acetic acid. It is insoluble in cold but somewhat soluble in hot acetone. It mixes with water to form an opalescent suspension from which it is precipitated by acetone. It is dextrorotatory having a specific rotation of about eight.

Sphingosine, the chief base, is an unsaturated amino alcohol, containing two hydroxyl groups, one primary amino group and one double bond, with the empirical formula of $C_{17}H_{35}NO_2$ and with the probable composition of $CH_3(CH_2)_{11} \cdot CH = CH \cdot CHOH \cdot CHOH \cdot CH_2 \cdot NH_2$. Sphingomyelin occurs in brain, kidney, liver, egg yolk, and in small amounts in blood and muscle.

Lecithin and cephalin. These substances contain, with one exception the same elementary constitutents—two molecules of fatty acid, one of phosphoric acid, one of glycerol and one of base. In lecithin the base is choline, in cephalin it is amino ethyl alcohol. They are found associated with each other in all tissues. Whether their chemical structure is the same apparently remains to be proven, but MacLean is of the opinion first expressed by Thudicum, that the arrangement of the con-

stituents in the molecule is different. Thus the arrangement in the lecithins would be

$$\text{Glycerol} \begin{cases} \text{Fatty acids} \\ \text{Phosphoric acid} \end{cases}$$
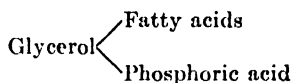
while in the cephalins it would be

$$\text{Phosphoric acids} \begin{cases} \text{Glycerol} \\ \text{Fatty acids} \end{cases}$$
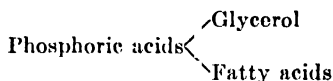
At any rate all workers are agreed that it is much more difficult to get the fatty acids from cephalin free from phosphoric acid than in the case of lecithin. The situation is further complicated by the fact noted by MacLean (28) that lecithin may be changed by the treatment of extraction and purification until it becomes insoluble in alcohol and thus passes for cephalin. True, cephalin, he states, is soluble in alcohol.

The number of lecithins or cephalins is limited theoretically only by the number of fatty acids, since each new arrangement of fatty acids would mean a new compound. Practically, however the number of different substances of this nature found in the animal body is probably limited to a very few, although very little information is available on this point. The phospholipide of cellular material is probably to be regarded as essential to the life of the cell since it is preserved in constant proportion even in extreme emaciation (29) (30). Its exact function is still unknown although, as indicated below, it probably has mainly to do with the metabolism of the fatty acids.

Properties. The lecithins and cephalins are soluble in the fat solvents with the single and characteristic exception of acetone. They are miscible with water forming cloudy solutions from which they may be precipitated by acetone. Ordinary lecithins and cephalins oxidize readily in air, turning brown and taking on a disagreeable odor. They have no definite melting point but decompose on heating. They combine with both acids and bases and form combinations with the most diverse substances —salts, proteins, carbohydrates,—most of which, are not to be

considered as chemical compounds but rather adsorption mixtures, and it is probable that lecithin exists in tissues in this type of combination. They undergo hydrolysis more readily than the fats.

In preparing them advantage is taken of these properties. Thus lecithin is separated along with cephalin from the other lipides by virtue of its insolubility in acetone. It is separated from cephalin by taking advantage of the insolubility of the latter in alcohol. It is separated from water-soluble impurities by solution in water and precipitation with acetone; from organic impurities by combination with cadmium chloride, etc.

Lecithin. The structure of lecithin generally accepted (Mac-Lean) is as follows:

$$
\begin{array}{l}
CH_2\ OOC\ R \\
|\\
CH.\ OOC\ R_1 \\
|\\
CH_2{-\!-}O \\
\qquad | \\
OH{-\!-}P{=\!=}O \\
\qquad | \\
\qquad O \\
\qquad | \\
\qquad C_2H_4 \\
\qquad \diagup \\
N{\equiv}(CH_3)_2 \\
\qquad \diagdown \\
\qquad\quad OH
\end{array}
$$
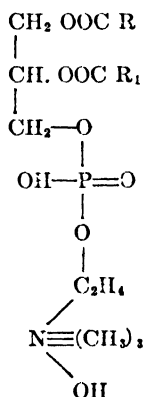
This is the asymmetrical form. A symmetrical form is possible, with the phosphoric acid radicle attached to the middle carbon of glycerol, but since all known lecithins are optically active the asymmetrical formula is probably the correct one. The mode of attachment of the choline to the phosphoric acid is still a matter of dispute, although the ester form of combination as above is generally accepted.

Lecithin has been synthesized by different workers, Grün and Kade (31), Grün and Limpacher (32) and most recently by Levene and Rolf (33). Grün and Limpacher indicate another possibility in the lecithin formula—the possibility of an anhydride form by loss of water from the phosphoric acid and chlorine

residues.   Levene, Rolf and Simms (37) removed one of the fatty acids (the unsaturated acid) by the action of cobra venom on lecithin, and from the lysolecithin so formed built up other lecithins.

The differences between various lecithins is largely if not altogether due to the fatty acids which they contain, and these have as yet been insufficiently studied.   As far as present information goes each lecithin contains one saturated and one unsaturated fatty acid.   Levene and Simms (34) found that the liver lecithins contained the saturated acids palmitic and stearic, and oleic and arachidonic as the unsaturated acids although linolic acid was not excluded.   Levene and Rolf (35) found that egg yolk contained oleic and small amounts of linolic and arachidonic acids.   In a lecithin prepared from the soy bean Levene and Rolf (36) found stearic and palmitic acids, and oleic, linolic and linoleic acids.   The proportion of unsaturated acids was relatively low as compared with animal lecithins.   As noted below the fatty acid composition of the animal lecithins may be altered to some extent by the fat of the food.

Cephalin.   The cephalins have been much less studied than the lecithins.   They are distinguished from them by their insolubility in alcohol, by containing aminoethyl alcohol in place of choline, and possibly by a difference in molecular structure. Otherwise their properties and behavior are much the same.

Like the lecithins they contain one saturated and one unsaturated acid in each simple molecule, and of these the saturated acid is apparently stearic.   The unsaturated acids of brain cephalin were found by Levene and Rolf (38) to be oleic and arachidonic.   MacArthur (39) found that cephalin from sheep and beef brain contained fatty acid in the following approximate proportions—stearic acid 30 per cent, oleic acid 55 per cent, cephalinic acid 10 per cent, and clupanodonic acid 5 per cent.   However, as MacLean has pointed out, no one else has found as high a percentage of oleic acid in cephalin.   Parnas (40) came to the conclusion that the only saturated acid of cephalin was stearic.

Galactolipides

Cerebrosides. These substances, of which only two (phrenosin and cerasin) are at all well characterized, are substances containing galactose, a base spingosine, and a fatty acid, but no phosphoric acid. They differ from each other only in the nature of the fatty acid which they contain, phrenosin containing phrenosinic acid $(C_{25}H_{50}O_3)$, and cerasin ligno-ceric acid $(C_{24}H_{48}O_2)$. In solubility they closely resemble sphinogomyelin, and the separation from this substance is difficult. They dissolve readily in hot alcohol, acetone, or benzene, but are almost insoluble in ether, hot or cold. They dissolve readily in pyridine. They occur in largest amounts in the brain, and are of interest to the biochemist because they contain galactose which is not known to occur in any other combination in the tissues, and also because they contain a sugar and a fatty acid in the same molecule, which is of interest from the fact noted below that the fatty acids, in the later stages of their metabolism, seem to require the assistance of the carbohydrates.

The significance of these compounds in the living body is unknown and their mention in the biochemical literature has had almost entirely to do with their separation and characterization.

DERIVED LIPIDES

Fatty acids

The important series of fatty acids are:

1. The saturated, straight chain series $C_nH_{2n}O_2$, including practically all the even numbered carbon atom acids up to and including C_{30}. The more commonly occurring ones in the natural fats are palmitic (C_{16}) and stearic (C_{18}) acids which occur in practically all. Palmitic acid is the most widely distributed, and quantitatively is the most important. Of the others which are of notable importance to the biochemist may be mentioned the lignoceric $C_{24}H_{48}O_2$ found in sphingomyelin and cerasin.

2. The series with one double bond $C_nH_{2n-2}O_2$—oleic or acrylic

series. The only practically important member of this series is oleic acid, although several other members of the series are known, for example, hypogeic (C_{16}), gadoleic (C_{20}), erucic (C_{22}) together with isomers of each, having the double bond in different positions.

Oleic acid is the most widely distributed of all the acids of the fats, and is also quantitatively the most important. It is found in several isomeric forms but the commonly occurring one has the constitution $CH_3(CH_2)_7CH = CH \cdot (CH_2)_7COOH$. Another oleic acid was found by Hartley (41, 42) among the fatty acids of liver, and has the double bond between the 6th and 7th carbons. It is interesting to note that he also found in liver a C_{18} acid with two double bonds, one between the 6th and 7th, and one between the 9th and 10th positions, the occurrence of which would be most readily understood by supposing that the ordinary oleic acid of the food or stores had acquired a new linkage between the 6th and 7th carbons.

The cis-trans type of isomerism is exhibited in ordinary oleic acid by treatment with nitrous acid, the liquid acid changing to the solid elaidic acid. This transformation takes place readily in the case of most other members of the series but strangely enough does not in the case of the isomers of oleic acid with the double bond in a different position. Oleic acid is quite stable in air as ordinarily kept, but becomes rancid when exposed to the combination of light, air and moisture.

The acids more unsaturated than oleic acid are found in vegetable oils and in animal tissues. In the former they are present as tri-glycerides (fats) while in animal tissues very little is present, as fat the larger part being as phospholipides. The presence of these more highly unsaturated acids in the vegetable oils gives them the important commercial property of "drying," i.e., of forming by oxidation a waterproof skin or varnish over surfaces on which they are spread as in painting. The unsaturated acids of animal tissues, although they oxidize in air in a similar way, become sticky instead of forming a smooth skin. These differences may probably be referred to differences either in the length of chain or position and number of the double bonds.

While oleic acid is quite stable in the presence of oxygen at ordinary or body temperatures, the more unsaturated acids take up oxygen and undergo other changes with a readiness dependent on the degree of unsaturation. Leathes has observed that it is rare to find fatty acids in the fat stores of the animal body more unsaturated than oleic acid, which be believes is due to the fact that oleic acid may be stored without oxidation at body temperature, while a more unsaturated fat cannot. When needed for combustion it is further desaturated, and probably combined with phosphorus.

3. *The Linolic Series.* $C_nH_{2n-4}O_2$. The known acids of this series are all C_{18} acids. They were studied first in linseed oil and have since been found to occur rather widely in animal tissues, for example in pigs' liver as shown by Hartley (42), and by recent work in other tissues such as blood (43), egg-yolk (35), muscle, etc. Except in the liver, and then only in relatively small amount, they do not occur in ordinary stored fat of mammals, but are found mainly as phospholipides or as esters with cholesterol.

The structure of these acids is not known. They react with alkaline permanganate in the cold in a similar way to oleic acid, forming hydroxy acids, and on further oxidation yield short chain acids.

Linolenic Series $C_nH_{2n-6}O_2$. A C_{18} acid of this series, or rather two isomeric acids have been prepared from linseed oil (44). Some light on its constitution was obtained by decomposition of the ozonide which yielded sufficient azelaic acid to account for half the molecule. In addition, malonic acid and propionic aldehyde were obtained. Traces of an acid of which the bromine derivative is insoluble in ether but soluble in benzene have been found in blood plasma.

Linolenic acid has been reported among the unsaturated acids of brain by Grey (45).

Other series. Of the acids of other series very little of biochemical importance is known.

Ricinoleic acid $C_{18}H_{34}O_3$ is the main constituent of the glycerides of castor oil. Its constitution is probably $CH_3(CH_2)_5-$

$CHOH \cdot CH \cdot CH = (CH_2)_7COOH$. It is optically active, having a specific rotation $\alpha_D = 6.67°$ (46). On oxidation with nitric acid it yields azelaic and sebacic acids.

Hydroxy acids of unknown composition have been found in brain by Grey (45) making up about 25 per cent of the solid acids. Two of the acids found were monohydroxy acids, and therefore cannot have been formed in the separation.

Certain cyclic fatty acids have come into prominence recently because of their therapeutic use in leprosy. These are the acids of chaulmoogra oil, mainly hydnocarpic acid $C_{16}H_{28}O_2$, and chaulmoogric acid $C_{18}H_{32}O_2$. The composition of these acids as indicated by the work of Power and Barrowcliff (47)[3] is

$$
\begin{array}{cc}
\underset{\substack{\displaystyle CH \\[-2pt] \diagup\!\!\diagup \quad \diagdown \\ CH \quad\; CH \;\; (CH_2)_n\, COOH \\ | \qquad | \\ CH_2\!\!-\!\!CH_2}}{} & \rightleftarrows \quad
\underset{\substack{\displaystyle CH_2 \\[-2pt] \diagup \quad \diagdown \\ CH\!-\!\!-\!\!C(CH_2)_n\, COOH \\ | \qquad\quad | \\ CH_2\!\!-\!\!CH_2}}{}
\end{array}
$$
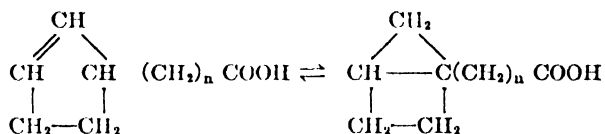
They take up only two atoms of bromine and are strongly optically active.

Odd carbon fatty acids. These do not occur in nature, but since the lower acids have been found to form sugar and not to form derivatives of acetone, their possible usefulness in diabetes has been suggested. Reports on the use of glycerides of margaric acid ($C_{17}H_{34}O_2$) indicate that they are apparently well utilized, but whether they will be found more useful than ordinary fats for diabetics is open to question (48) (49).

Clupanodonic acid, the 18 carbon member of the series $C_nH_{2n-8}O_2$ has been obtained from Japanese sardine oil, herring, and whale oil, and appears to be contained in all fish oils. Arachidonic acid, $C_{20}H_{32}O_2$, was found in pig's liver by Hartley (42), and later in the lecithin from the same source by Levene and Simms (34). Amounts generally less than 5 per cent of the total fatty acid, of acids giving bromine derivatives insoluble in ether and benzene have been found in the cholesterol

[3] Recent work of R. L. Shriner with Roger Adams indicates that these compounds exist in only the first form. The paper will soon be published in J. Am. Chem. Soc.—Editor.

ester fractions of blood plasma, and in the lecithin (acetone insoluble) fractions (50).

Levene has found archidonic acid in brain cephalin and lecithin (38).

Solubility. The lowest members of the various fatty acid series up to C_6 are miscible with water in all proportions. Caproic acid is soluble in water at 15° to the extent of about 0.9 per cent, and the solubility decreases rapidly with increasing length of chain. All the saturated acids above lauric acid are practically insoluble in water. In hot absolute or 95 per cent alcohol all fatty acids are soluble, but from palmitic acid upwards all are sparingly soluble in cold alcohol.

All fatty acids are soluble in ether, chloroform, benzene, etc. All except the hydroxy fatty acids are soluble in petroleum ether (distilling below 60°).

The hydroxy acids are more or less soluble in water depending on the number of hydroxyl groups, thus octohydroxy arachidic acid is easily soluble in water (Lewkowitsch), hexahydroxystearic more difficultly soluble, while tetrahydroxystearic acid requires 2000 parts of boiling water for solution. The highly hydrolylated acids are insoluble in ether and difficultly soluble in alcohol. The dicarboxy acids are more soluble in water than the corresponding monocarboxy acids, and in general less soluble in the fat solvents. The solubilities of the hydroxy and dicarboxylated acids are of particular importance in biochemistry, since all the reactions of living beings take place in a watery medium and probably in water solution. The fact that the fats are insoluble in water imposes a difficulty on their utilization, and makes important any forms which are soluble in water. The hydroxy acids have been found in living things, and dicarboxy acids are among the products of oxidation in vitro of the unsaturated acids, although their presence in the tissues of animals has not been demonstrated (see below).

Salts of glycocholic and taurocholic acids (bile salts) dissolve fatty acids, and greatly increase the solubility of the soaps formed during digestion of the fats (51).

Oxidation. Oxidation of oleic acid yields a variety of prod-

ucts depending on the oxidizing agent and the conditions under which oxidation takes place. With potassium permanganate in alkaline solution at low temperatures it yields a dihydroxystearic acid, and at a higher temperature breaks at the double bond giving two 9 carbon acids, azelaic, a dicarboxy acid and pelargonic, a monocarboxy acid, the stages in oxidation being probably as follows (Leathes):

$$CH_3 \cdot (CH_2)_7 \cdot \overset{H}{C} \cdot \overset{H}{C} \cdot (CH_2)_7 \cdot COOH$$
$$OH \quad OH$$

$$CH_3 \cdot (CH_2)_7 \cdot CO \cdot \overset{H}{C}(CH_2)_7 \cdot COOH$$
$$OH$$

$$CH_3 \cdot (CH_2)_7 \cdot CO \cdot CO \cdot (CH_2)_7 \cdot COOH$$

$$CH_3 \cdot (CH_2)_7 \cdot COOH \quad HOOC \cdot (CH_2)_7 \cdot COOH$$
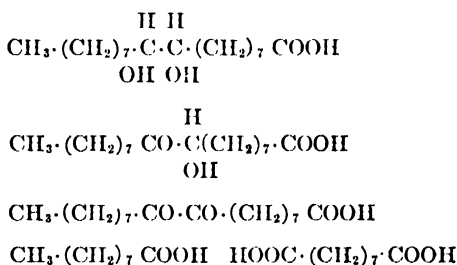
It is assumed that the position of the double bond does not shift during the oxidation, and the above is accepted as evidence that the double bond is in the middle of the molecule. That the double bond in oleic acid may be mobile and that therefore the above assumption may be incorrect is believed by Armstrong and Hilditch (52). Ozone acting on oleic acid forms first an addition product, an ozonide, which on heating with potassium alcoholate yields azelaic and pelargonic acids, giving further evidence that the double bond is in the middle of the molecule.

The fact that the double bond is thus shown to be a point of weakness in the chain, at least during oxidation, in vitro is taken by Leathes to indicate that during oxidation in the animal body a similar breaking of the chain takes place. Exception may be taken to this assumption as Leathes himself has pointed out in the fact that there is no evidence for the formation of either azelaic or pelargonic acids in the body, and for other reasons to be discussed below.

Hydrogenation. The unsaturated acids take up hydrogen with the aid of catalysts at the double bonds and become saturated. Sabatier and his co-workers, especially Senderens, were the first to show that finely divided metals and particularly

nickel were the best catalysts. Since that time the process has become of great commercial importance in changing comparatively inedible oils, such as cottonseed oil, into valuable articles of diet. As far as can be determined, the hydrogenated fats are just as well utilized by the animal body as the natural fats (Langworthy). A review of the work on hydrogenation of oils has recently been published by Sabatier (54).

Halogen absorption. The halogens, and particularly iodine, are readily absorbed at the double bonds, and under certain conditions the absorption is quantitative so that the halogen absorption value (iodine number) constitutes one of the most important means of study of the fatty acids. The more unsaturated acids (three and four double bonds) form halogen absorption derivatives which are insoluble in most fat solvents, and this property serves for their identification and approximate determination.

Sterols

The alcohols belonging in this group are those found combined in the waxes, and of these the only ones directly connected with life processes are cholesterol, its isomers and derivatives.

Cholesterols and phytosterols. These are isomeric compounds differing from one another in crystal form, melting point, degree of optical rotations, melting point of esters. Cholesterol is characteristic of animal tissues and phytosterol correspondingly of plant tissues.

Cholesterol. Formula $C_{27}H_{46}O$, constitution (55)—

$$(CH_3)_2:CH \cdot (CH_2)_2 \text{---} C_{17}H_{26} \text{---} CH{=\!=}CH_2$$
$$\mid \text{\textasciitilde\textasciitilde}$$
$$CH_2 \cdot CHOH \cdot CH_2$$
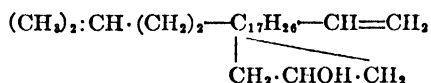
This formula indicates the presence of only one double bond, but since it absorbs two molecules of ozone there appears to be a second one, perhaps in the ring nucleus. The nature of the nucleus is not known, but the evidence available points to its being related to the terpenes (56). Cholesterol is insoluble in cold water, sparingly soluble in cold alcohol, readily soluble in hot alcohol and in fat solvents generally. Its melting point is

about 148°C. It is levo-rotatory, the rotation varying some-what with the solvent. For ether $\alpha_D^{15°} = 31.1°$ (Hesse). On exposure to light and air it slowly undergoes changes—its melting point is lowered, its solubility changed, and its color reactions rendered indefinite.

Its iodine absorption value varies with the solution used With Hübls' reagent it gives practically theoretical values (67 to 68 as compared with 65.8, the theoretical value.) Wijs solu-tion gives erratic results.

Methods for detection and determination. The methods which are most useful for small amounts are:

1. *The Liebermann-Burchard method* depending on the color developed in a chloroform solution of cholesterol by acetic an-hydride and sulfuric acid. A fine green color is finally produced, which under exactly defined conditions is quantitative. Based on this reaction a considerable number of methods for its deter-mination in blood and other body fluids have been developed, but the fact that there are so many methods indicates that the determination by color production is not particularly satis-factory. Reasons for the difficulty have been indicated, among them the fact that rosin acids and terpenes give similar reactions (57), that the tint and development of the color is influenced by light and temperature (58), and that the esters of cholesterol influence the tint (59). Nevertheless the colorimetric methods take relatively little time as compared with the precipitation method (noted below), and when conditions are carefully con-trolled give results of sufficient accuracy for most purposes.

2. *The Windaus digitonin precipitation.* Cholesterol unites quantitatively with digitonin to form an addition product which is practically insoluble in alcohol or ether. The esters do not combine with digitonin, so that it is possible by this means to make a quantitation separation of free cholesterol from its esters (60) (61). This useful method is at present almost unavailable owing to the high price of digitonin.

The gravimetric determination of cholesterol in tissues is beset with difficulties owing to the fact than when separated in the ordinary way in the "unsaponifiable" fraction after

hydrolysis of the tissue with alkali, it is contaminated with much other material from which it is difficult to separate it.

Concerning its distribution in the animal kingdom Doree (62) writes as follows: "It is found in the tissues of all animals examined. In warm blooded vertebrates it is the only sterol found but in lower animals and insects somewhat variant forms are present. They all have the same formula and differ only in crystal form and in the melting points of their dibromides and acetates. The unsaturated linkage and the −OH which Hausmann (63) found to be essential for its antitoxic functions are found in all forms. Cholesterol never occurs in plants and in animals appears to be formed almost exclusively from the phytosterol of the plants although recent work indicates that synthesis is possible."

Isocholesterol differs from cholesterol in being dextrorotatory (α_D = +60° in ether), and in having a lower melting point (136°). It is less soluble in cold alcohol than cholesterol and gives a yellow color with the Liebermann-Burchard reagent. It occurs in wool wax.

Phytosterols are closely related to the cholesterols in composition and have many similar properties. They hold a position in plants corresponding to cholesterol in animal tissues. Phytosterol palmitate has been found in corn pollen (64).

The distribution of the sterols in various fats and oils has been reported by Steuart (65).

METHODS OF STUDY OF TISSUE LIPIDES

Two general procedures are available for removal of lipides from tissues:

Extraction—removal of the lipides from the tissues in approximately the form in which they exist there. In the experience of the writer the solvent which gives most nearly complete extraction is boiling alcohol. It has two disadvantages—it extracts other substances than the lipides, and the heat probably decomposes some of the more sensitive ones. Nevertheless it is probably superior to all others for the purpose, since it can

be applied directly to the tissue without previous drying and almost inevitable oxidation, and because it penetrates the tissue readily, breaking up whatever loose combinations there may be between lipide and other cellular constituents. Cold alcohol is preferred by many because there is less danger of decomposition of the lipides. It takes much longer than the hot solvent and gives a less complete extraction. Others of the fat solvents are used for special purposes, e.g., acetone to remove cholesterol and free fat, leaving the phospholipides. Solvents like ether and chloroform extract very little from fresh tissues, and while they give better results with dried material, the extraction is never complete. Preliminary treatment of the tissue with alcohol results in a better extraction with these solvents. The purification and examination of the individual lipides is a matter of great difficulty, and the procedures cannot be described in a brief review. The reader is therefore referred to special articles (66).

Hydrolysis—destroying the tissue by the use of strong alkali, then extracting the separated fatty material. This procedure is to be recommended when a quantitative measure of the lipide content is required, but it has the disadvantage of giving very little information regarding the lipides as they are in the tissue. Two fractions are obtained—the fatty acids and the "unsaponifiable matter," the latter consisting of the sterols and a number of unknown substances, part of which are probably related to them (67). The procedure was first made use of by Liebermann, and developed in detail by Kumagawa and Suto (68), and later by Lemeland (69).

Methods for the determination of the physical and chemical characteristics ["constants"] of the fatty acids have been well worked out, but since they are given in all good treatises on the chemistry of the fats they will not be described here.

PHYSIOLOGICAL ASPECTS

This section of the review will deal with the fats and related substances more particularly in their behavior in the animal organism.

Digestion

Fat differs from the other foodstuffs in that it has very few forms which are water-soluble and probably for this reason an entirely different mechanism is made use of in the animal body for its transport through the intestinal wall and in the blood and tissues (70). In its digestion it follows the general rule of breaking down into its constituent elements, glycerol and fatty acids just as the proteins are reduced to amino acids and the carbohydrates to monosaccharides and while absorption in undigested form cannot at present be excluded, the facilities for digestion are ordinarily so adequate that it is questionable whether any escapes hydrolysis. Enzymes which can accomplish the splitting (lipases) are to be found in the gastric and pancreatic secretions and to a less extent, although still in notable amounts, in the secretions of the glands of the intestine itself. These lipases are all in water solution and can therefore act only on the surface of the fat particles and splitting can take place to a notable extent only when the available surface of the fat is large—as when emulsified. The main emulsifying agent in the intestine is soap formed by the union of the free fatty acid in the fat with the alkali of the bile and pancreatic secretions. The fatty acid present in small amounts in all food fats is increased by the processes of cooking and by the gastric lipase until when the fat reaches the intestine it has enough free fatty acid in it to ensure good emulsification. Mucin in the bile and other secretions and lecithin in the bile act to increase the stability of the soap emulsion.

Ordinarily there is little fat splitting in the stomach, first because a soap emulsion cannot form in an acid medium and second because the gastric lipase is destroyed by acid. Appreciable hydrolysis takes place only when the fat is in emulsified form as in milk and when enough protein or other neutralizing agent is present to reduce the gastric acidity to a point where the lipase destruction is slow. Another condition under which fat splitting may take place in the stomach is when for any reason, such as excess of fat in the food, emptying of the stomach

is delayed, then intestinal fluids containing bile and pancreatic secretions back up into the stomach.

In the intestine the most important factor in digestion and absorption not excepting the pancreatic secretion, appears to be the bile, since when it is missing, fat absorption falls to a lower level than when bile is present and pancreatic secretion is absent. The great importance of the bile rests in its power of dissolving soaps and free fatty acids in which solution they appear to be readily absorbed. The important constituents of the bile which accomplish this end are the bile acids, glycocholic and taurocholic acids (71).

The absence of pancreatic lipase appears to have no great effect on the *hydrolysis* of the fat since owing to the presence of lipases in the intestinal secretion this is practically complete whether pancreatic lipase is present or not (72) and the reason why so much fat escapes absorption under these conditions is probably that hydrolysis is greatly delayed and owing to re-absorption of bile which is known to take place, there is no bile salt left in the intestine to aid in the passage of the fatty acids through the absorbing cells.

During their passage through the intestinal wall the fatty acids and glycerol are resynthesized into fat, in this way differing again from the other foodstuffs which apparently reach the blood stream and are delivered to the tissues as "building stones." It is generally assumed that the agent producing the synthesis is the same agent—the pancreatic lipase—which brought about the hydrolysis. The resynthesized fat does not go directly into the blood stream but passes by the lymph stream through the thoracic lymph duct into the venous circulation. It is still an unsettled question as to whether any part of the fat is absorbed directly from the intestine into the blood stream. Only about 60 per cent can be recovered from the thoracic duct where it empties into the circulation, which leaves 40 per cent to be accounted for. Attempts to demonstrate direct absorption of fat into the blood leaving the intestine have not given satisfactory results (73) (74). Recent work goes to show however, that there are pathways between the lymph and venous cir-

culations other than the main opening of the thoracic duct, a finding which will go far to explain the discrepancy. Thus Lee (75) after ligation of the thoracic duct found that connections were established between the lymphatic duct and the azygos vein or its branches also with the right thoracic duct. He gives also a good review of the literature showing that similar results have been reported previously, concluding that it is well established that the lymph and therefore the absorbed fat does not necessarily all enter the venous system at the base of the neck. These findings are borne out by the recent work of Eckstein (76)

As regards other lipides—lecithin when fed has sometimes been found to give a slight increase in the blood lecithin (77) and in the lecithin of the chyle (78). More recent work has failed to support these findings (76) and goes to show that lecithin, like the fats and simple esters is hydrolysed in the intestine and the resulting fatty acids built up into fats during absorption. Simple esters such as the ethyl esters of the ordinary fatty acids are hydrolyzed in the intestine and the fatty acids are built into glycerides, no evidence of the original ester or its contained alcohol being found in the chyle (79, 80, 81).

Choice of fat during absorption

A statement is being carried in the literature and attributed to Arnschink (82) that the fatty acids of the feces have a higher melting point than those of the fat fed and that therefore the intestine exercises some choice in the absorption of fat. There is no such statement in Arnschink's article and no other support to be found in the literature. The fat of the chyle is however not always the same as the fat of the food. Frank (80) found after feeding ethyl stearate that the melting point of the fatty acids was much below that of either stearic acid or tri-stearin. Bloor (83) after feeding olive oil found that the fat of the chyle melted around 30°. These differences may mean either that the absorbed fat was diluted with body fat from some nearby source or that chemical changes take place—such as desaturation in the case of the stearic acid and saturation in case of oleic acid.

After feeding cocoanut oil Raper found that the fatty acids of chyle showed a higher average molecular weight than that of the oil fed, which he believed indicated that the lower acids of the oil probably reached the blood stream as soluble salts (84).

Digestibility and absorbability of fat

There is a prevailing belief among dietitians that certain fats are more digestible than others, that the vegetable fats and the recently exploited hydrogenated fats are less well utilized by the animal body than the animal fats. In an investigation of this point, Langworthy (53) made use of 23 animal, 34 vegetable and 6 hydrogenated fats in feeding experiments on human beings. The results showed very little difference in the behavior of the fats studied. In general the utilization was found to be inversely proportional to the melting point, the high melting fats being more difficult of utilization. His results show that, aside from melting point, the origin of the fat is not of importance to its utilization.

After long feeding, fat may be less well utilized than at first. Thus Pettenkofer and Voit (85) in a 58 day feeding period of 500 grams meat and 200 grams fat daily to a 32 kilo dog found that the feces contained as high as 38 per cent of fat while at the beginning absorption was complete (98 per cent).

Parenteral absorption

Fat as such or preferably as an emulsion injected under the skin or into the abdominal cavity is absorbed in considerable amounts. It passes into the lymph system and much of it enters the blood by the usual channel—the thoracic duct (86) (87).

Homogenized fat injected intravenously produces a sudden rise of blood fat of 100 per cent or more, then a slow fall. Not over 44 per cent of the injected fat was present in the blood at any time (88). Fat in coarser suspension appears to be treated like other suspended foreign matter—it is removed rapidly, the coarse particles in the lungs, the finer ones in the liver, spleen and bone marrow.

Cholesterol

Free cholesterol alone is absorbed but little if at all from the intestine. When dissolved in fat or fatty acid it is slowly absorbed with partial esterification. Müller (89) found that when cholesterol was fed either free or as esters (together with fat) there was an increase of both in the chyle, the proportion between the two remaining approximately the same as is found normally in blood plasma indicating that esterification or hydrolysis may take place in the intestinal walls. Wacker and Hueck (90) found that both free and bound cholesterol could be increased in rabbits' blood by feeding cholesterol, but they could not get an increase in the blood of cats and dogs. Grigaut and L'Huilliere (91) succeeded in producing these effects in dogs by feeding cholesterol. Knudson (92) found that during the absorption of olive oil there was a marked increase in cholesterol esters but no increase in total cholesterol in the blood. In later work (93) he fed pure cholesterol and cholesterol esters to dogs and found both were absorbed but in every case the increase was in the *free* cholesterol and not in the esters. These results are in disagreement with those of Gardner and co-workers (94) who found that when cholesterol was fed to rabbits there resulted an increase in esterified as well as free cholesterol. Knudson believes that the exclusion of fat from his diets is responsible for the failure of the esters to increase.

Fat—blood

The fat passes from the intestine into the thoracic duct and to the blood in the form of a very fine suspension which persists for a few hours and then disappears. The fine particles of fat are about 1μ in size, are visible with the highest power of the microscope and a count of the number in a given volume gives a measure of the rate at which fat is reaching the blood (95). The measure is only approximate since the number in the blood at any time is the resultant of the number entering and the number leaving the blood during the period of absorption. During the period in which absorbed fat is present in the blood the

lipide phosphorus of the blood increases (96) (97) (98). Cholesterol has been found to increase (generally late in the period of absorption) by some workers (99) but most others have not found any increase unless cholesterol was present in the fat fed.

The manner in which the fat leaves the blood is not known. During fat absorption it accumulates in the blood, in the liver, and to a less extent in other organs. Colored fat in fine emulsions injected into the circulation is found to collect in the liver, bone marrow, spleen and muscles in the order named in which respect it behaves like other foreign material (100).

Since fat is hydrolyzed before passing the intestinal cells, the question has been raised whether a similar hydrolysis was necessary before it could pass into the tissue cells (101). Such a process would require the presence in the blood or in the cells where fat was being deposited, of enzymes capable of splitting the fats. Such has been shown not to be the case (102) and fat passing the tissue cell walls as such to and from the blood, probably does so without the aid of lipases.

In this connection confusion has arisen because of the universal presence of an enzyme which splits simple esters such as ethyl butyrate and glycerides of the lower fatty acids readily, but acts only slowly on the glycerides of ordinary fat. This enzyme is called lipase by many workers. Since it also hydrolyses lecithin and possibly cholesterol esters it is probably of considerable but enough evidence (103) has accumulated to show that it is not a true lipase and should not be so called. The name suggested by Loevenhart for this enzyme is "Esterase" which seems to the reviewer a good one and since there is no longer any question about there being two enzymes, the distinction should be emphasized. While esterases are widely distributed in animal tissues (104) lipases appear to be confined to the pancreas and intestine.

LIPIDES IN THE TISSUES

Stored fat

It has long been known that fat was one of the forms in which energy was stored in plants and animals and the nature of the

fat and the way in which it was formed and laid down have been the object of scientific and commercial interest.

In animals fat may occur in all organs and tissues but the three most important places of permanent deposit are the intermuscular connective tissue, the abdominal cavity, and the subcutaneous connective tissues. In plants the seeds and fruits and in certain cases the roots are rich in fat and in winter, fat is to be found in the trunks of trees.

The nature of the stored fat in warm blooded animals has been extensively studied. It consists ordinarily largely of a mixture in varying proportions of the glycerides of the three fatty acids, palmitic, stearic, and oleic acids. Esters of various other fatty acids such as lauric, myristic, and linolic are sometimes present in small amounts and are probably to be referred to the food.

In cold blooded animals the stored fat contains a larger proportion of the unsaturated acids than does the fat of warm blooded animals.

In plants there occurs the greatest variety of combined fatty acids, practically all the known *even* numbered fatty acids occurring in combination in plant products.

Stored fat in animals originates in the food, representing either material synthesized from carbohydrate or protein or transferred more or less directly from the fat in the intestine.

Each species of animal under normal conditions lays up a fat which is to a considerable extent characteristic of the animal; thus it is not difficult for even the amateur to distinguish between lard and beef tallow and the chemist has been able to work out a set of characteristics for each animal and vegetable fat by means of which he is able to distinguish one from the other with a considerable degree of accuracy. In plants there is only one possible source of the stored fat—carbohydrate and as consequence the "constants" of vegetable fats are much more definite than those of animal fats. In animals the fat of the food may by forced feeding be transferred to the fat stores with little if any change but when the animal has a normal choice of food the fat which is stored is quite different from that

of the food. Modifications may be brought about in the fat absorbed in the following known ways: (a) by changes during absorption, (b) by choice as to which of the constituents of the food fat is burned and which stored, (c) by admixture with fat synthesized from carbohydrate. Very little is known about any of these methods of modification so that their relative importance cannot be estimated. Regarding (a), although changes have been shown to take place in both hard and soft fats, the way in which the change is produced, whether by dilution with fat from bodily sources or by chemical change, is not known. Fat synthesized from carbohydrate is "hard" fat as exemplified in the practice among hog-raisers of "finishing" the animals by a period of grain feeding to harden them, i.e., to produce a firm fat. Scientific foundation for the practice has been furnished by the work of Anderson and Mendel (105) who found that with a preponderance of carbohydrate in the diet a characteristic hard fat was produced, while with a preponderance of various oils, a fat corresponding to these oils could be stored. Anderson (106) showed in addition that in adult animals which had been raised on various oils the oily stored fat may be changed to a hard fat by feeding with starch. Jackson (107) lists the fats of ordinary feeds in the following order of their ability to produce a soft fat—most effective linseed, then soy bean, maize, beechnut, cottonseed, wheat, pea, oat, rice, peanut, barley, rye, and bean. Shioji (108) showed that the phospholipides of the tissues may also be somewhat changed by the fat of the food but to a much less degree than the stored fat.

Fat storage in the liver

The liver of animals ordinarily contains considerable amounts of carbohydrate and not much fat. The fat which it contains is, however, considerably more unsaturated than the fat of the stores. Under certain conditions—fasting, phosphorus poisoning in certain diseases, and to a certain extent after fat feeding the fat content of the liver increases greatly. Fat has been found to accumulate in the liver of young animals before birth.

Imrie and Graham (109) studied the fat content of the livers
of embryonic guinea pigs throughout the period of gestation
and found that from the time when the embyro is 35 to 40 grams
weight to the time of birth the fat content increases from 2 to
3 per cent up to 16 to 18 per cent of the moist tissue and has a
comparatively high iodine value. After birth the fat diminishes
rapidly in the first 48 to 72 hours. Many reasons have been
offered for the accumulation of fat in the liver. Of these one of
the earliest, that of fatty degeneration—the transformation of
liver protein into fat—has been abandoned since exact methods
have provided no evidence to support it. Another was that of
an antagonism between glycogen and fat. When the liver is
full of glycogen, fat cannot be deposited there in notable amounts,
but when the glycogen is exhausted or low, fat flows in to take its
place (110). The flow of fat to the liver in diabetes and in
general in carbohydrate starvation has been taken as support
for the idea that fat is transformed to carbohydrate, which is
believed to take place in diabetes by many workers (chiefly
European) (111). It should be noted that carefully controlled
work in this country gives little support to this view (112).
In the writer's opinion the most rational reason for the accumu-
lation of fat in the liver is given by the Leathes hypothesis of
fat metabolism, according to which the flow to the liver is a
normal process since the first stage of fat catabolism—desatura-
tion—takes place there (see below).

Biochemical synthesis of fatty acids

It has long been known, practically, that animals can synthe-
size fat from the carbohydrate of the food and the scientific
proof has not been difficult to supply. In plants formation
from carbohydrate is the only method of fat formation. Never-
theless the details of this all-important synthesis are practically
unknown.

Pasteur observed the formation of butyric acid by bacteria
from glucose and also from lactic acid. Nencki explained this
synthesis in the light of the fact that lactic acid very readily

breaks down to acetaldehyde. Two molecules acetaldehyde condense by the aldol condensation to β hydroxy butyric aldehyde and this by simultaneous oxidation and reduction passes over to butyric acid. Raper (113) showed that small amounts of caproic and caprylic acids are formed at the same time, indicating that the aldol condensation may be repeated with the formation of higher fatty acids.

A. Loeb (114) found, that when a surviving liver containing but little glycogen was perfused with a solution of acetates in blood, diacetic acid was formed, indicating a direct condensation. Since, as noted above, acetic acid is a product of the break-down of lactic acid and therefore probably of glucose, these findings indicate that the aldol condensation or one of a similar nature may be responsible for the synthesis of the fatty acids in the animal body. An objection has been raised to the aldol condensation as applied to the synthesis of the higher fatty acids by Smedley (115) who showed that the higher aldehydes when condensed in vitro tend to form branched chains instead of straight chains. Other facts bear out the assumption that the fatty acids are built up as they are broken down—two carbon atoms at a time. Thus practically all the naturally occurring fatty acids contain an even number of carbon atoms although odd carbon fatty acids are well utilized by the animal organism as shown by the experiments on feeding the lower odd carbon acids mentioned above and the recent work with glycerides of margaric acid ($C_{17}H_{34}O_2$) (116). In milk fat, and cocoanut oil, practically all the even numbered fatty acids from butyric acid up to stearic are present, representing all stages of the progressive synthesis, two carbons at a time.

The suggestion by Emil Fischer that the higher fatty acids are formed by direct condensation of the sugar molecules with reduction and oxidation has no chemical or biological evidence to support it but is nevertheless interesting since the most widely distributed and, from the point of view of quantity the most important fatty acids are those of 18 carbon atoms such as would be formed by the condensation of three glucose molecules.

Synthesis from proteins

It has been shown by feeding experiments with experimentally diabetic animals that about two-thirds (58 per cent) of the protein molecule is convertible into carbohydrate (117). Since carbohydrate is readily convertible into fat it follows that protein should be also. The difficulty of demonstrating the conversion is great, owing to the fact that, because of the bulk of ordinary protein food and also because of its stimulating effect on metabolism, animals cannot readily be made to eat enough to provide a surplus. Then again all protein food contains some fatty material from which it is almost impossible to free it without destroying the protein. Moreover, all animals contain a store of glycogen which is a potential source of fat. One of the most convincing experiments on this point was carried out by Cremer (118). After starving a cat for several days so as to eliminate the glycogen as far as possible, the animal was given all the lean meat it would eat—450 grams per day. For eight days the whole carbon retention was 58 grams, corresponding to a glycogen production of 130 grams. The animal was found, however, to contain only 35 grams of glycogen, leaving the remainder of the carbon therefore as fat.

In recent work Atkinson, Rapport, and Lusk (119) report as follows: When the glycogen reservoirs are low, ingestion of large quantities of meat results in deposition of glycogen. Further meat feeding results in retention of both fat and glycogen while on stuffing with meat, fat alone was formed. After a carbohydrate meal the evening before (glycogen stores full), ingestion of meat produces fat. In an earlier experiment it was found (120) that after a meal of 1000 grams of meat the respiratory quotients of the fifth, six and seventh hour were 0.842, 0.845, 0.845. Computations on the basis of the metabolism of protein which was the equivalent of 1.44 grams of urinary N per hour, appeared to indicate a retention of material which would have shown respiratory quotients in the successive hours of 0.708, 0.688, 0.685, or approximately the same as fat, confirming the earlier work of Atkinson, and Lusk (121). For

the three hours by direct calorimetry 85.32 calories were found. By indirect calorimetry, if the retained carbon be calculated as having been deposited as fat, 83.58 calories may be calculated as the heat which should have been expected to arise. Had the carbon been retained as glycogen the calculated heat production would have been greater (about 4 calories per hour).

In the lower forms of animals and in plants formation of fat from protein can be more easily demonstrated. Weinland (122) showed that the larvae of the blow-fly (calliphora) could split peptone to amino acids, remove the amino and carboxyl groups and form fatty acids from the fragments. Bacteria and Fungi can form fat from protein (123).

On the other hand much of the evidence for fat formation from protein must be rejected. Thus the supposed increase of fat in ripening of cheese was found not to be the case (124) but rather the fat content diminished. The "adipocere" found in animal remains buried in wet, impervious soils was believed to be formed by decomposition of body protein. The work of Ruttan and Marshall (125) has shown that this substance has nothing to do with protein but is formed from the fat present in the animal at death. It consists of a mixture of cholesterol and fatty acids in crystalline and amorphous form and calcium, magnesium and ammonium soaps of palmitic and stearic acid. The oleic acid of the fat seems to disappear except as it is represented by a small amount of hydroxy stearic acid. The material left is light but bulky and gives the impression that most of the body has been transformed into this waxy substance.

As regards the fatty degeneration of tissues during which fat was supposed to be formed at the expense of protein it has been shown that the fat content of the tissue is generally no greater than normal and in those cases where it is greater, as is often the case in the liver, the extra fat can be shown to have originated in the fat stores (126) (127). The apparent increase of fat in degenerated tissues is due to a setting free of fatty material which in normal tissues is "built in" in such a way as to be invisible, unstainable by histologic methods and not extractable with ether.

Tissue lipides

As has just been noted, there is always a large proportion of the fatty materials of tissues which cannot be seen with the microscope, cannot be stained by the usual fat stains and cannot be extracted by the ordinary fat solvents such as ether, chloroform or benzene, but may be removed, although much of it with difficulty, by alcohol either cold or hot. The nature of this lipide material and its relationship to the fat of food and stores constitutes one of the important problems in the field of fat metabolism at the present time.

The most widely distributed of these constituents are the phospholipides of various composition which are present in practically all tissues and in blood. Their function (see below) is assumed to be in connection with the intermediary metabolism of the fatty acids since they carry in combination the more unsaturated acids found in the body. Cholesterol, either as such or as its numerous isomers, is also universally distributed and in the form of its esters with various fatty acids is one of the main lipides of blood plasma. Cholesterol esters are found in tissues and organs but only in such small amounts that their presence there may be accidental as the result of adherent blood plasma. Practically all the other known lipides have been prepared from animal and plant tissues.

In addition to the lipides normally present in tissues others may be deposited in abnormal conditions. Thus the "anisotropic" fat of the pathologists appear to consist characteristically of combinations of cholesterol with the fatty acids and may be produced by excessive feeding of cholesterol (128) (129). Under these circumstances the deposits take place first in the Kupfer cells of the liver and in the adrenals, corpus luteum, spleen and endothelium of the blood vessels. The suprarenal glands are characterized by the large amounts of cholesterol and cholesterol esters which they contain. Cholesterol crystals may be found in any tissue that is undergoing slow destruction, especially where absorption is poor, accumulating as one of the least soluble of the cell constituents.

The lipide percentages of normal blood and tissues are characteristic of the tissue and remain relatively constant over a wide range of bodily conditions including starvation, (130) (131) although with the progress of the latter certain differences appear. In severe diabetes the percentages of blood lipides are generally considerably above normal and in some cases very much above (132) (133). The mechanism of the lipemia of diabetes has been discussed in detail (134).

THE OXIDATION OF THE FATS IN THE LIVING BODY (INTERMEDIARY METABOLISM)

The glycerol

The available evidence indicates that glycerol is utilized in the same way as the carbohydrates. Thus when fed to completely phlorizinized animals it is excreted as sugar (135) (136) and in the consideration of the foodstuffs as to whether they produce or prevent the production of the acetone compounds it is found to behave as an anti-ketogenic substance (137).

The fatty acids

The manner of disposal of the long chains of the fatty acids offers greater difficulties. One of the probable early stages in fat utilization is the formation from it of phospholipides by replacement of one of the fatty acid groups by a phosphoric acid complex—generally either phosphoric acid-cholin as in the lecithins or phosphoric acid-aminoethyl alcohol as in the cephalins. The evidence regarding the phospholipides as intermediary compounds in the utilization of the fats is, first, the universal presence of these compounds in living tissues and organs, second, the increase of lipide phosphorus in the blood during fat absorption when the blood contains much extra fat (alimentary lipemia) (138) (97), third, the increased values for lipide phosphorus in lipemia of other origins (139), and fourth, evidence of formation of milk fat from phospholipide of blood. Meigs, Blatherwick and Cary (140), workers were able to show as a result of the analysis of the blood before and after

passing through the milk gland of the cow, that the fat of milk originated mainly if not entirely in the phospholipide of the blood. In work reported at an earlier date Jordan, Hart and Patten found in cows that a diet low in phosphorus resulted in a lower milk fat production than when the phosphorus supply was adequate. The change affected mainly the glycerides of the volatile and soluble fatty acids—which would require more phosphorus for lecithin formation than the higher acids (141). Lastly it has been possible to show that the phospholipides of the hen's egg may be influenced by the fat of the food (142) and that the fat of the food may have some although slight influence on the phospholipides of the tissues (108). McCollum (142) found with hens that on a fat-free diet the phospholipides of egg yolk had iodine values of 34 to 35 while on normal mixed diet the iodine values were 63 to 64.

The advantages of the phospholipides as intermediate stages in the utilization of the fats are obvious. They mix readily with blood plasma or even with distilled water, forming a dispersion which while not a true solution provides a convenient means of transport of the insoluble fats in a watery medium such as the blood and tissues of the animal body. They readily form loose conbinations with various substances such as salts, glucose, and proteins indicating that they may be a very important stabilizing factor in the complex of living protoplasm. They are chemically more reactive that the fats, undergoing hydrolysis (to at least a considerable extent) more readily and are also more readily oxidizable, which may mean no more than that of the fatty acids they contain are more readily oxidized than those of the fats.

The evidence, while it does not prove that the phospholipides are intermediate stages in the utilization of the fats indicates that such a stage is a strong possibility.

Regarding other early stages in the working up of the long chains of the fatty acids, the theory of Leathes is practically universally accepted. It is stated as follows: "The fat is transported to the liver, unsaturated unions are there introduced into the fatty acids and possibly there, too, the complex compounds

of fatty acids with phosphorus and nitrogen are built up" (143). The data on which Leathes based his theory are as follows:

Hartley found (41) that the fatty acids of the liver, kidney and heart of several animals including man were to a considerable extent acids ot a series more unsaturated than oleic acid, having iodine absorption values of 115 to 135 while the fatty acids of the fat stores in the different animals ranged between 35 and 65. In the later part of his work he paid particular attention to the identification of the fatty acids in these organs and found that in addition to the saturated acids, palmitic and stearic, which composed about half the acids, there were present an oleic acid with the double bond between the 6th and 7th carbon atoms, a linolic acid $(C_{18}H_{32}O_2)$ with the double bonds between the 6th and 7th and the 9th and 10th carbons and an acid with four double bonds $C_{20}H_{32}O_2$ which has since been called by Levene "arachidonic acid." Arachidonic acid was present to the extent of about 10 per cent of the total fatty acids while there was more linolic that oleic acid. Hartley found also that the unsaturated acids were mainly combined in lecithin and similar complex substances.

Other facts which engaged Leathes' attention were, that in poisoning with phosphorus, chloroform, phlorizin, mineral acids, etc., in starvation and in many pathological conditions (in which an important factor may have been starvation) that the total fatty acid content of the liver which was not ordinarily more than three per cent of the moist weight might reach values up to 20 per cent (144) (145). It was also shown that the greater the fatty acid content of the liver the lower was the iodine value and the more nearly it approached the values for stored fat, indicating that the extra fat in the liver under these conditions was fat brought from the depots. Putting together these observations of mobilization of fat to the liver and the presence there of an unusual proportion of unsaturated acids, Leathes made the generalization that transport of fat to the liver was for the purpose of desaturation and was a normal step in fat utilization. Direct evidence of the desaturating power of the liver was obtained (146) by first determining the iodine value

of the fatty acids of the liver of rats on a normal diet, then feeding a fat of relatively high iodine value (cod-liver oil) and again examining the liver fatty acids. They were found to have an iodine value considerable higher than that of normal liver fatty acids and higher (over 30 per cent) than that of the cod liver oil fed. These experiments showed also that during fat feeding there was an increase of fat in the liver. Similar results were later obtained by Joannovies and Pick (147). Raper (84) obtained further evidence of the desaturating power of the liver. A comparison of the iodine value of the volatile fatty acids of the livers of cats with and without cocoanut oil feeding showed that the iodine absorbing power of the volatile fatty acids of the liver was increased after the feeding, indicating that the volatile fatty acids of the cocoanut oil of 10, 12, or 14 carbon atoms were desaturated in the liver. Hartley had stated that the unsaturated acids of liver were mainly in combination with lecithin and similar complex substances. Kennaway and Leathes were able to show (148) that the acetone soluble fraction of the lipoids of liver—consisting mainly of fat—contained fatty acids with iodine values much higher than those of adipose tissue (often double the values or more), indicating that the desaturating power of the liver was not limited to the phospholipides but extended to the fats also.

Leathes did not try to exclude the possibility of desaturation or phosphorization in other organs and tissues, but believed that both processes and especially desaturation were carried out mainly in the liver. The evidence in support of his theory regarding these early stages of fatty acid metabolism is perhaps not as extensive as might be desired but as far as it goes gives excellent support to his modestly expressed generalization.

Very little is known about the extent to which desaturation is carried. In the blood and most animal tissues, the most unsaturated acid found in quantity is a tetra-unsaturated acid identified by Hartley and Levene (149) as arachidonic acid. Not more than 10 per cent of the acids were found to consist of this one. An acid with three double bonds apparently does not exist in measurable amounts, except in the brain (45), while two

bond acids and of course single bond acids are most prevalent. Acids more unsaturated than the four bond acid have been reported only in the brain and in traces.

Regarding the final stages in the break-down of the fatty acid chains the prevailing conception of the method is that they are first oxidzed at the β carbon atom from the carboxyl group, producing β hydroxy or more probably β ketonic acids and then lose the terminal pair of carbon atoms yielding acetic acid and a fatty acid of two less carbons, the process being repeated until the chain is destroyed. The evidence supporting this conception has been reviewed many times and so need be only briefly referred to at this time. It is based largely on results obtained with phenyl derivatives of the fatty acids, by the use of which it has been shown (150) that the fatty acid side chains are oxidized away in this manner. The conclusion that this is the normal method of oxidation of the fatty acid chains is supported by much other evidence. Thus Embden (151) (152) and his co-workers perfused surviving livers with blood containing even numbered carbon fatty acids containing 6, 8, and 10 carbon atoms obtaining diacetic acid—which could have been produced only by β oxidation. Odd numbered acids did not yield diacetic acid. In various conditions which may be grouped under the general head of lack of available carbohydrate—starvation, diabetes, continued vomiting, etc.—the acetone compounds, acetone, diacetic and β oxybutyric acids are excreted in the urine. These are fatty acid derivatives oxidized in the β position and are regarded as originating mainly in the fatty acids of the fats. The objection that α oxidation and not β oxidation is the common result of oxidation of the fatty acids in vitro was answered by the experiment of Dakin (153) who showed that when neutralized butyric acid was oxidized in vitro under approximately the conditions in the living body, i.e., at about body temperature and with hydrogen peroxide, diacetic acid and acetone were obtained. When the reaction was carried out at higher temperatures the diacetic acid was converted into acetone by loss of carbon dioxide. This reaction was extended by him to higher fatty acids and it was found that every normal higher fatty

acid when neutralized and warmed with hydrogen peroxide gave the corresponding ketone containing one less carbon atom. This reaction demonstrated the occurrence of β oxidation in vitro in the clearest fashion. No good objection has yet been raised to the theory and it remains as the best explanation of the final stages of the oxidation of the fatty acids.

Accepting desaturation as the first stage in the catabolism of the fatty acids and β oxidation as the final stage, what can be said about the steps coming between?

Leathes' opinion was that since the double bonds constituted a point of weakness, oxidation with formation of hydroxy acids and subsequent breaking of the chain would take place in the animal body just as these processes take place in the laboratory with oxidizing agents such as alkaline permanganate. The resulting short chain acids would then be taken care of by β oxidation. Hydroxy acids, although of relatively frequent occurrence in plants, have been reported in the animal body only in the brain (Grey) so that they are probably not of great importance as intermediate steps. Further evidence that the hydroxy acids are not products of oxidation of the unsaturated acids in the animal body has been supplied by Dakin (154) and he is of the opinion that they are not formed, or at any rate not to any important extent. Oxidations in the animal body are limited by the fact that they must be carried on at a constant and relatively low temperature in a neutral medium and with reagents no stronger than the organic peroxides so that the analogy with laboratory reactions cannot be carried too far. Evidence from the behavior of the short chain acids which would be formed by the breaking of the long chains confirms the opinion of Dakin. The short chain fatty acids when fed to normal animals disappear without traces. When fed to animals rendered experimentally diabetic by phlorizin the odd carbon fatty acids yield glucose in proportion to the amount of propionic acid which they would yield by β oxidation (155) and the even carbon acids under the same conditions yield a certain proportion of diacetic and β hydroxybutyric acids and acetone. That odd carbon fatty acids are produced by

breaking the long chains seems unlikely, since feeding fat to experimentally diabetic animals or to diabetics does not produce any sugar (156). Lusk also showed that work sufficient to double the fat catabolism in phlorizinized animals did not increase the sugar output (157). As regards the formation of even-numbered, short chain acids, it is known that these yield acetone compounds in the completely diabetic organism, but since the greatest quantity of acetone compounds ever reported was in the proportion of one molecule of the acetone derivative to one molecule of fatty acid (158) the formation of short-chain even-carbon acids seems equally unlikely since otherwise more acetone compounds would be obtained.

Dicarboxy acids are formed by oxidation of unsaturated acids in vitro. Our information about the behavior of these acids in the animal body is, however, slight. Oxalic acid is resistant to oxidation, malonic and succinic acids are readily oxidized, tartaric acid and glutaric, less readily, while both these acids produce a severe nephritis (159). Baer and Blum (160) reported that adipic, pimelic and suberic acids had the same effect as glutaric in inhibiting sugar secretion in phlorizinized animals and probably, as Rose has pointed out, because they are also nephropathic. Rose believed that the toxic action on the kidney is due to slow oxidation.

A. I. Ringer (161) found that malic and succinic acids yielded large amounts of glucose in phlorizinized animals while glutaric acid yielded neither sugar nor acetone compounds. The available evidence thus goes to show that three and four carbon dicarboxy acids may be used by the animal body but the higher acids only with difficulty if at all. In general they seem to behave in the same way as the monocarboxy acids. Taken altogether, it would seem that the conception of the breaking of the long chains into shorter ones before final oxidation should not be adopted at the present time.

Although the available evidence does not indicate that the long chains are broken yet the presence of double bonds in the chain undoubtedly renders β-oxidation easier, whether the bond is at the point where β oxidation would take place or in the

position next to it, since, as was shown by Knoop's experiments with phenylalanine and tyrosine α oxidation does not hinder and probably aids β oxidation.

The mechanism of oxidation of the fatty acids as far as is known at the present time may be summed up as follows: The stable fatty acids of the food or stores are made less stable by desaturation, a process which takes place mainly if not entirely in the liver. Further reactivity is conferred by phosphorization of the glycerides. The long chains are then shortened two carbon atoms at a time by β oxidation, probably with the aid of organic peroxides, at least to the four carbon stage where a different type of oxidation involving the simultaneous oxidation of glucose appears to be required in most animals. The two carbon fragments are oxidized to carbon dioxide and water.

Ketogenesis and antiketogenesis

The peculiarity in oxidation of the fatty acids referred to in the last paragraph now calls for attention. In the absence of available carbohydrate, many animals including man are unable to oxidize completely the fatty acids past the four carbon stage and the unburned products, diacetic acid, β hydroxybutyric acid and acetone (the acetone or ketone 'bodies' appear in the excretions. Two of these substances are fairly strong acids and all three are believed by some (162) to be toxic in addition to their acidity. The formation in quantity of these acids which must be neutralized before excretion, puts a severe strain on the ability of the organism to supply alkali for their neutralization and results are often fatal owing to depletion of the fixed alkalies necessary for respiration. The dog and probably carnivorous animals in general are immune to this type of poisoning, a result undoubtedly of long adaptation to the lack of carbohydrate and the presence of large amounts of fat in their diet. Instances of similar adaptation of human beings and other animals to a high fat diet are available in the literature. Thus Wigglesworth in experiments on rats with a straight fat diet found marked ketosis which reached a maximum on the third day, then subsided and adaptation was complete on the fifth

day. Sodium bicarbonate (6 per cent) prevented the adaptation, causing an increased output of lactic and β hydroxybutyric acid, indicating that much alkali may interfere with the normal oxidation of fat (163). Folin (164) found that obese individuals when fasted excreted much less acetone compounds on the second and succeeding fasts than on the first one. The amount of actual or potential carbohydrate necessary in the diet of human beings in order to avoid this "acidosis" or "ketogenesis" has been the subject of many investigations, of which the most extensive have been those of Woodyatt (165) and Shaffer (166).

Without going into the elaborate details of this work, which has been reviewed recently by Shaffer (166), the results may be summed up as follows: One molecule of glucose or its equivalent in other substances which yield sugar in metabolism (antiketogenic substances) is theoretically able to secure the complete combustion of two molecules of fatty acid or other substance yielding ketone compounds (ketogenic substance); but owing probably to uneven distribution and uneven metabolism in different parts of the body it is necessary, in order to be certain of avoiding the production of the acetone derivatives, to allow one molecule of antiketogenic substance, such as glucose, in the diet to one molecule of ketogenic substance such as fatty acid. These results have already been applied satisfactorily in clinical practice (167), (168) (169), which is proof of their essential soundness. Shaffer has also contributed much toward the elucidation of the manner in which the carbohydrates assist in the combustion of these fragments of the fatty acids. finding that the combustion (170) (171) of diacetic acid in the presence of glucose is probably preceded by a condensation of the Knövenagel type between some derivative of glucose and the diacetic acid, the condensation product being much more easily oxidized than the diacetic acid alone.

Acid intoxication

The condition of acid intoxication, due to depletion of fixed alkali noted above, is in man almost always associated with

incomplete combustion of fatty acid residues and for this reason a brief reference should be made to it.

Excess of inorganic acids, HCl, H_3PO_4, which cannot be destroyed or detoxicated, produce in man the following symptoms —stupor, coma accompanied by excessively active respiration (air hunger) with normal oxygen content of blood and low CO_2 values. The urine contains increased quantities of calcium, magnesium, potassium, sodium and ammonia. In dogs the ammonia alone is much increased and this animal is relatively resistant to acid poisoning. Acidosis is therefore an impoverishment of the blood and tissues of bases, thus reducing the capacity to combine with and eliminate CO_2 and other acids formed in metabolism. Practically, acidosis results either from defective oxidation of organic acids formed in metabolism or defective elimination due to impaired kidney function. The first factor is of main interest to us here because the most important source of organic acids is in the failure to oxidize completely the fatty acids.

In man, poisoning with organic acids is not an infrequent occurrence although confined largely to one disease—diabetes mellitus. In this disease the final stage is often coma in which the symptoms are strikingly similar to those noted above— asphyxia, due not to diminished ability of the blood to carry oxygen but a diminished ability to carry carbon dioxide, the reason for which is the production in large amounts of β hydroxybutyric and diacetic acids together with acetone and a resultant depletion of fixed alkali. These compounds are closely related chemically and the acetone and β hydroxybutyric are generally regarded as derived from the diacetic acid, which is thought to be the primary product (172) (173), an opinion which is given substantial support by the work of Wilder (174) who found that while β hydroxybutyric acid was formed in the animal body after injecting diacetic acid, diacetic acid was not formed as the result of corresponding injections of β hydroxybutyric acid.

These acids are not formed in appreciable amounts in the organism as long as a minimum quantity of carbohydrate is being utilized. This carbohydrate may be available as such

or be formed from protein. In the normal individual a lack of available carbohydrate occurs practically only in fasting but in the diabetic it occurs as the result of inability to utilize carbohydrate even though adequate amounts may be supplied.

The excretion of these acids in man often reaches 15 to 20 grams per day and as much as 150 to 200 grams has been claimed. β hydroxybutyric is normally 60 to 80 per cent of the total (175). In normal blood Marriott (176) found about 4 mgm. of β hydroxybutyric and 1.5 mgm. of acetone and diacetic together, while in blood of diabetic coma the figures were 45 and 28 mgm. per 100 cc. of blood respectively.

The tissues and especially the blood are kept at a reaction very near the neutral point (pH 7.3 to 7.4) and the extreme variations consistent with life are only a few tenths either way. In addition to preserving the reaction within these narrow limits, provision must be made of a certain reserve of fixed alkali necessary to take care of the carbon dioxide formation and excretion. To keep the reaction of blood and tissues within these narrow limits of reaction noted and to keep a sufficient "alkali reserve" in the face of acid production various devices are made use of in the animal economy. The more important ones are (1) excretion of a urine as acid as possible, the limit in humans appears to be a pH of about 5 (177); (2) neutralization of the acids by ammonia, making use for the purpose of nitrogen which would otherwise be excreted as urea (178); (3) use of excess alkali in the food and as a last resort the use of the fixed alkali of the blood and tissues down to a point where respiration can no longer be carried on. Animals vary a great deal in their ability to protect their fixed alkali. Herbivorous animals have little power of resistance while carnivorous animals such as the dog are very resistant. Man comes in between these two extremes and, when carbohydrate is not present in the food or cannot be made available from it, as in diabetes, is in danger of death due to depletion of the alkali necessary for respiration.

Intermediary metabolism of other lipides

Very little is known regarding the behavior of the other lipide substances in metabolism.

Cholesterol appears to be necessary for life and is ordinarily supplied in the food in adequate amounts either as such or in the form of other sterols which the body changes into cholesterol. Animals, or at least young animals, appear to be able to synthesize cholesterol. Thus Thannhauser and Schnaber (179) found that the cholesterol of hen's eggs increased on incubation. Stepp (180) reported that pigeons could synthesize cholesterol. Beumer and Lehmann (181) in experiments with new born puppies found that the increase in bodily cholesterol was equal to twenty times the amount in the food. Similar results have been obtained by Knudson (182) with rats. Gamble and Blackfan (183) found that much more cholesterol (up to three times as much) was excreted by infants than was present in the food. There is evidence that when the intake is inadequate it is retained and used over again (184).

Fat excretion

A small amount [generally not over 3 per cent] of fatty material is normally present in the feces of animals and it is ordinarily regarded as material that has escaped digestion. Evidence has, however, accummulated which goes to show that it (185) (186) (187) is not unabsorbed material but represents largely an excretion, whether directly from the blood by way of the intestinal secretions, or indirectly as desquamated cells from the intestinal tract. The possibility of its origin in the bacteria present in the intestine and composing a notable percentage of the fecal mass cannot be excluded but since the bacteria usually present in the intestine contain very little fat they are probably not of great importance as sources of fecal fat. Recent work (188) (189) has shown that the lipide output in the feces, while to some extent related to the amount and kind of fat in the food is in general remarkably independent of it and approaches in composition that of the blood. Under certain conditions such as lack of bile or pancreatic secretion, diarrhorea, and when the food contains a large amount of bulky, indigestible material, fat may escape digestion or absorption. The excretion of fatty material is almost entirely as fatty acids, very little unhydro-

lysed fat appearing except when the secretion of bile is stopped. Of the excretion of other lipides very little is known except of cholesterol.

Excess of cholesterol in the food is apparently largely excreted in the bile. McMaster (190) found that the amount of cholesterol in the bile was greatly increased by feeding it, while in fasting the output is greatly reduced. D'Amato (191) found that cholesterol feeding (as brain and egg) caused a small but constant increase of cholesterol but the increases were so small as to indicate that the bile was not the main path of excretion. The most authoritative statement on this point is that of Gardner (192) as follows: Cholesterol is eliminated by the liver and reabsorbed from the intestine, and whether any is finally excreted depends on the intake. Man reduces it to coprosterol and β cholestenol although some escapes unchanged. In man there is an ordinarily negative balance of 0.3 gram per day so that there is probably some synthesis.

FATS IN THE DIET

Fats are the most concentrated of the food stuffs, about 90 per cent of their weight being available for combustion. Their energy value is consequently the highest of all the food stuffs.

The heats of combustion of the natural food fats vary from 9.0 calories per gram for cocoanut oil to 9.50 calories for goose fat. Castor oil has a value of 8.84 calories per gram, boiled linseed oil 8.81 calories and spermaceti (a wax) 9.95 calories per gram (Lewkowitsch). The average value used in computations of energy in animals in 9.3.

Because of their concentrated nature they are made use of largely in plants and animals as a form in which energy may be stored. In the human diet they are valuable as convenient and concentrated sources of energy, reducing the bulk of the food intake, and adding the factors of flavor and platability as well as for certain valuable vitamins. In view of our present knowledge of tissue constituents, the statement formerly made regarding them that "they cannot serve for the upbuilding or renewal of tissues" must be revised, since such substances as

lecithin are probably as important constituents of tissue as protein.

The fact that fats can be synthesized from other food stuffs such as carbohydrates has raised the question as to whether they can be dispensed with in the diet. Experiments on this point have been carried out by Drummond and Coward (193) who have shown that young rats may grow normally from weaning to maturity on diets as free as possible from neutral fats, indicating that fats are dispensable constituents of a diet, provided the fat soluble vitamin is present in other food stuffs. The same conclusion had been reported by Hindhede (194).

Along with a little carbohydrate [probably to ensure their complete combustion] they act as efficient sparers of protein. Their utilization stimulates metabolism ["specific dynamic action"] less than protein but more than carbohydrate. After ingestion of fat the heat production [over the basal] rises gradually to the sixth hour to a maximum 30 per cent over the basal metabolism then falls slowly to the basal level, which is reached 10 hours after consumption, following the curve of changing fat content of the blood and therefore probably the concentration of metabolites available (195). The increased heat production is entirely at the expense of the ingested fat, the basal respiratory quotient averaging 0.84 and after fat ingestion becoming 0.79. Calculation showed that the amounts of protein and glycogen oxidized during two sets of experiments were identical so that the extra heat production after giving fat was derived from fat itself.

The use of fat in the diet is limited by its difficulty of digestion and combustion and ordinarily it does not compose more than one-fifth of the total energy requirement. In diabetes where carbohydrate [and therefore most of the protein] cannot be utilized it may form a much higher percentage (up to 80 per cent) of the requirement and be well utilized. As has been pointed out many times, however, a distinction must be made in these cases between fat eaten and fat burned since a certain proportion of the large amount of fat fed is probably stored.

In starvation the animal must depend largely on its store of

fat. The carbohydrate stores [glycogen] are exhausted in the first two or three days, then the energy requirement falls chiefly on the fat with a minimum of body protein, and the animal lives as long as his fat stores last. As these near exhaustion, body protein alone is left and since its energy value is less than half that of fat and is moreover, as tissue, mixed with about three times its weight of water, the animal soon dies. The composition of the organs most essential to life such as the heart, kidney, and brain is preserved almost to the end.

VITAMINS ASSOCIATED WITH FATS

Three of the five probable vitamins are associated with fats in natural products and so enhance their importance in diet. These are the fat soluble, or growth vitamin A, the antirachitic vitamin D, and the newly discovered but fairly well established reproductive or fertility vitamin E. The study of these substances has been carried on largely by the use of the domesticated white rat which lends itself readily to this type of experiment, reacting to feeding in most ways like the larger animals and by its short life cycle making it possible to get results quickly. The main disadvantage of this animal so far as is concerned with these vitamins is that it is relatively resistant to rickets. The literature on this subject is very large and since it has been excellently reviewed recently only the outstanding points and the later work will be mentioned (196). (Note: For the more recent developments in this field the reviewer has drawn largely on an unpublished summary made by Dr. H. A. Mattill of this institution.)

The vitamin A is associated with growth and well being and its lack is shown by failure to grow, and by lowered resistance to infection of which the most frequently manifest sign is xerophthalmia—a drying up of tear glands accompanied by purulent infection. The presence of vitamin A in a given food is best tested by determining the amount which will bring about resumption of growth and disappearance of the eye symptoms. Cod liver oil and most other fish liver oils have been found to be the richest source of vitamin A. The fat of egg yolk, alfalfa,

clover, green vegetables, carrots, yellow corn, butter, and milk contain notable amounts. It is low in root vegetables, seeds, and nuts. The amount in milk fat is dependent on the amount in the food of the animal.

Vitamin A is more easily destroyed by oxidation than by heat and the accompanying material appears to influence the rate of destruction. Thus heated animal fats and unheated lard and certain vegetable fats appear to destroy it (197). Young animals require more of the vitamin than old, females more than males, and reproduction and lactation increase the requirement. It may be stored in the organs and tissues of the body, especially in the liver.

The active substance is associated with the unsaponifiable fraction of the fats and is apparently not injured by mild processes of saponification. It is not cholesterol and the active substance may be distilled at low pressure without destruction and may be concentrated in this way (198).

Vitamin D: The disease rickets is characterized by an abnormality in the deposition of calcium and phosphorus in the bones and teeth and the presence of vitamine D is best demonstrated by the beginning of a zone of calcification (line test) in the long bones. The identification of this vitamin has been delayed because of a similarity in distribution with vitamin A and because vitamin D also shows a growth promoting function. The distribution of vitamin D is much the same as vitamin A but the content of the two is generally widely different. The amount of vitamin D varies widely with the history and antecedents of the product which brings us to the most striking characteristic of the vitamin which is its connection with ultraviolet radiation. Light rays of $313\mu\mu$ or shorter appear to function in place of the vitamin or probably to be the cause of it. Inactive food products of various kinds, but particularly the fats and oils may be activated by exposure to direct sunlight or to ultraviolet radiation and, furthermore, the substance may be produced in the living animals by the same treatment (199) (200) (201).

Cholesterol, itself inactive, becomes an active antirachitic

substance by irradiation. Even the excreta of animals may be activated.

As may be imagined from the above, little can at present be said about the chemical nature and relationship of vitamin D, but like A it appears to be associated with the unsaponifiable fraction of the fats rather than with the fats or fatty acids themselves.

Vitamin E (named by its discoverer, H. M. Evans, Vitamin X) is related to the reproductive function and its absence is shown in female rats by the failure to carry their young to term although impregnation and fertilization may proceed normally. In male rats the germinal cells of the testicles degenerate. The female rat is the best test animal and the presence of the vitamin in a given food product is determined by its ability to bring about normal reproduction.

Wheat germ and dried lettuce leaves are the richest sources of vitamin E yet found. It is found in butter fat but not in cod liver oil.

It is a definitely fat-soluble substance and is again associated with the unsaponifiable fraction but is not cholesterol. It is relatively sensitive to oxidation (202) (203) (204) (205).

Summing up the present knowledge of the vitamins in their relation to the fats it appears that they are not connected with the fats or fatty acids as such but are always found in the unsaponifiable residue and are not cholesterol or any other known substance, although they may be related to some of these. Attention is thus strongly drawn to this hitherto little studied group of substances, indicating that their investigation will well repay the effort of the chemist.

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ELEMENTS WITH ANOMALOUS VALENCES[1]

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OLDER HISTORY

Kekulé, who derived his ideas of valence largely from the study of carbon compounds, concluded that valence of all elements, as he found it to be in the case of carbon, is a fundamental property of the atom as invariable as the atomic weight itself. Very soon, however, it became apparent that Kekulé's position was not tenable, but that, as Frankland had suggested, valence, with some elements, is not fixed but variable. None the less, the fixed quadrivalence of carbon was accepted and for nearly half a century this idea remained the basis and the principal guide for all work in the vast field of organic chemistry.

With the enunciation of the periodic law, the mooted question of the variable character of valence received, so it seemed at that time, its answer from the periodic table of the elements. It became obvious that, generally speaking, the first three groups show a distinctly fixed valence capacity, from 1 to 3 respectively; in the fourth group the elements are equally divided between those with unvarying quadrivalence and those which can function with a valence lower than four. Beginning, however, with the fifth group, practically all the elements were judged to possess variable valence, ascending in number to 5, 6, 7, and 8 respectively, or descending to 3, 2, 1, according to whether oxygen or hydrogen was the measure of valence.

And yet, a certain regularity was read even into the variation itself. In the carbon group, the elements tin, lead—and later also germanium—were found to function either as quadrivalent

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or bivalent, but not trivalent. In the fifth group the variation was again by two, as As^{III} and As^V, and so in the oxygen group, as S^{II}, S^{IV}, and S^{VI}, and finally in the halogen group, where the valence is 1, 3, 5, and 7. Exceptions to this general rule were not unknown, as for instance $TiCl_3$ and NO, but they were so few in number as to be disregarded. There was known, in addition, a large class of compounds the existence of which could not very well be explained solely on the basis of atomic valences. These complex compounds,—hydrates of salts, double salts, etc. —were looked upon as "molecular compounds," in which normal molecules were held together not through atomic valences, but through some other force, through "molecular" attraction.

RECENT HISTORY

Such was the state of the valence idea some thirty years ago, when several new, independent, and diverse currents of thought were initiated which finally brought about a profound change in the views concerning the immutability of valence. Only some of these currents can be mentioned here.

COÖRDINATION THEORY

Werner's "Coördination Theory" assumes that in all the complex salts, the hydrated salts, the basic salts, and even in such simple compounds as NH_4Cl, the molecule is made thus: The principal atom is located in the center and around it are symmetrically packed, or "coördinated" a certain number of other atoms or groups, and each of the coördinated units is directly united to the central atom. Usually the coördination number is 6 and these 6 coördinated atoms or groups occupy the six corners of an imaginary octohedron; less frequently the coördination number is 4, and still less, 8; but it may also be 1, 3, 5, or 7, depending upon a variety of factors. In addition to the coördinated atoms or groups which are situated in the immediate vicinity of the central atom, the molecule contains several additional atoms or groups. These however must lie outside of the coördinated complex, since they may become readily dis-

sociated away as ions from the complex. They lie, therefore, in a secondary zone, and the coördinated complex functions in respect to them as a single unit or ion. The following instances will serve as illustrations: $[Co(NH_3)_6]Cl_3$, $[Co(NH_3)_4Cl_2]Cl$, $[Co(NH_3)_3Cl_3]$, $[CdI_4]K_2$, $[SiF_7](NH_4)_3$, $[Mo(CN)_8]K_4$ etc.

In the desire to make the new views compatible with the teachings of the older valence hypothesis, Werner attempted to differentiate between the "true" valences of the central atom, as predetermined by its position in the periodic table of the elements, and those new additional valences which the atom presumably acquires in the formation of the coördinated compound. He named them accordingly principal or primary valences and auxiliary or secondary valences. Later, however, this distinction was found to be too indefinite, and with the recognition of the electronic nature of all valence phenomena, the artificial division into auxiliary and principal valences had to be abandoned. The successful application of the coördination theory in the classification and the study of thousands of inorganic and of many organic compounds is evidence that the theory contains a truly important generalization. Moreover, the theory withstood the same severe test to which the stereochemical theories in organic chemistry had been subjected, namely,—the ability to predict the definite number of space isomers possible as well as the particular circumstances essential for the occurrence of optical isomerism in this group of inorganic compounds. The fact that the theory lends itself with only slight modifications, to a restatement[2] in terms of the modern electron valence theory, is further evidence in favor of the essentially sound basis upon which the coördination theory rests.

What then is the operating valence of the central atom in these coördinated compounds? If we assume, as we must, that there is no intrinsic difference between the principal and the auxillary valences within the coördination complex, then obviously the active valence of the coördinating atom is the same as its coördination number, and is, consequently, nearly always greater

[2] (a) J. J. Thompson, The Electron in Chemistry, Franklin Institute, 1923; (b) G. N. Lewis, Valence, The Chemical Catalog Company, 1923.

than the regular orthodox valence.[3] Thus, among the many important consequences of this theory, the following one is particularly apposite in the discussion of the mutability of valence: We have become accustomed to the idea that the valence capacity of an element is not delimited by the position of the element in the periodic table, but that it is a distinctly variable function and can rise to a much higher number than we have ever supposed in the past that it could do.

<div align="center">VALENCE ELECTRONS</div>

Of course, the greatest influence upon the chemist's views of valence came from the revolutionary transformation of the physicist's ideas concerning atomic structure, which transformation was initiated, among other causes, when J. J. Thompson in 1897 determined the mass of the electron, and showed that the nature of the electron is always the same from whatever element it may come.   There is general agreement on the main point. In the center of the atom is a nucleus of positive electricity, and surrounding this an equal amount of negative electricity which is carried by electrons as many in number as is represented by the atomic number of the element.   Only those electrons, however, which lie in the peripheral zone are directly engaged in the establishment of chemical bonds between two atoms—these alone are the "valence electrons."   The number of valence electrons in the elements is a periodic function of the atomic numbers and varies from 0 up to 8, and the elements which occupy corresponding positions in the periods contain an equal number of valence electrons.   Eight therefore is the maximum number of valence electrons, and this represents the most stable configuration.   So chemical reaction, union among atoms, must tend

[3] Werner originally postulated that those groups which are located within the complex are linked each directly to the central atom by principal or auxiliary valences, while those in the secondary zone, always by principal valences either directly or indirectly to the central atom.   This postulate, coupled with the statement that auxiliary valence is unable to effect the union of univalent radicals, may lead one to the somewhat ambiguous interpretation that the central atom in some instances assumes a valence even greater than that represented by the coördination number of the atom.   See for instance the formulas in Thomas' "Complex Salts," Van Nostrand, p. 22, 1924.

towards the establishment of a sphere of eight valence electrons around the atoms which participate in the reaction. But even with the allowance that the valence electrons alone and no other electrons are concerned in the creation of chemical bonds between atoms, there still arises a multitude of perplexing questions when one tries to picture to himself the *modus operandi* of this process. If an active bond is created through the complete transference of one valence electron from atom A to atom B, then evidently the maximum bonding capacity of atom A is determined by the number of its valence electrons, and there is no inherent reason why atom A should not exhibit, under specific experimental conditions, every possible variation in valence between its maximum and zero. The same applies to the second atom in this transaction, the operative valence of atom B being measured by the number of electrons it has acquired from atom A. On the other hand, if it be assumed that a chemical bond can also be established when atoms share electrons, be it either in the statical or the dynamical sense, then the question arises how many electrons must be thus shared for each bond, how many atoms may partake simultaneously in the sharing of the same electrons. It becomes impossible to predict the maximum bonding capacity of an atom unless some arbitrary postulates be introduced which would limit the variable factors mentioned. G. N. Lewis and Kossel, have advanced the happy postulate that a bond consists of a *pair* of shared electrons, shared only by *two* atoms. With this postulate the hypothesis of shared electrons has proven exceedingly useful. And yet one wonders why one electron cannot be shared by two or more atoms; one wonders whether the active triatomic hydrogen may not have the structure $\overset{\text{HH}}{\underset{\text{H}}{\because}}$. May not the molecule of phosphorus, P_4, be $\overset{P\,..\,P}{\underset{P\,..\,P}{}}$? If the author reads him correctly, J. J. Thompson assumes the existence of bonds of some such nature in the hydrated salts, polymers of formaldehyde, the possible existence of unstable $(CaCl_2Cl)^-$.[4]

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[4] See the very suggestive critical review in Main Smith's "Chemistry and Atomic Structure," Ernest Benn, Chapter XIII (1924).

Accept whichever view of valence mechanism we wish, it is now obvious that the idea of fixed valence for some elements and variable for others is untenable. Every element must be capable of forming compounds through the operation of all its valence electrons, or through the operation of only some of these. Experimental conditions alone must be the determining factor whether a given element will act in its maximum capacity, in some particularly stable valence, or in any other supposedly anomalous valence.

TRIVALENCY OF CARBON, FREE RADICALS

It would be desirable to point out in this connection still other important recent factors that have contributed materially towards the development of our views concerning the mutability of valence capacity. The exigencies of the present occasion, however, make this impossible within the time limitation, since, by all precedent, it is incumbent upon the speaker to say something of his personal contribution in the field under discussion, be that contribution, as it is in this case, ever so slight.

With the discovery, in 1900, of the curious substance which has become known as triphenylmethyl, the idea of fixed valences received a very serious set-back. Here was a substance which, according to all standards of experimental evidence, behaved as if it contained one of its 19 carbon atoms in the molecule in the trivalent and not quadrivalent state. It constituted the first definite example of anomalous valence in the behavior of the very element that had, up till then, shown an unvarying constancy in the tens of thousands of its compounds. Many other similar compounds have been prepared since,—not far from a hundred triarylmethyls—and the "trivalence" of carbon is now looked upon as a normal manifestation, for we know fairly well when to expect it and how to recognize it when it does occur. In the early discussions, the historical interest of these substances was emphasized rather than their theoretical bearing. The implied existence of a substance with a carbon atom in trivalent state, was equivalent to stating that an uncompleted molecule can exist, or, in the older language, that a "radical" is a reality and not

merely a symbol and a figment of the imagination. It brought back to memory the bitter controversies of the long forgotten past. It recalled the stirring events in the history of chemistry when Gay-Lussac, in 1815, announced the preparation by him of free cyanogen, in which, so he thought, he obtained the first true "compound element" or radical, and that he thus vindicated Lavoisier's prediction of some 30 years prior. It recalled the days of Liebig and Wöhler's investigation in 1832, of the "benzoyl" radical; the vigorous and at times somewhat one-sided participation of Berzelius in these controversies, of Berzelius the law-giver in the chemistry of his times. It recalled the joint proclamation of Liebig and Dumas, in 1837, who professed to see locked up in these radicals the very mysteries of organic nature. It brought back to memory the discovery by Bunsen in 1842 of the presumed radical "kakodyl;" by Kolbe, in 1849, of "methyl," and by Frankland, in 1850, of "ethyl" and "amyl." It recalled the passionate and caustic expressions of Gerhardt and of Laurent in their bitter opposition to the theory that radicals can exist; it recalled, finally, the fading away of that theory with the advent of the valence hypothesis and the general acknowledgment at that period of the invariable quadrivalence of carbon, so strenuously advocated by Kekulé.

ANOMALOUS VALENCE IN SOME OTHER ELEMENTS

This represents the historical aspect of the triphenylmethyl episode. A more permanent significance of the triarylmethyls as a class lies in the fact that the study of these compounds has opened the way for analogous studies also with elements other than carbon. By means of methods that are similar to, or not much different from, those which have been employed in the preparation of the free triarylmethyl radicals, it has been fairly well established, through the labors of many investigators,[5] that compounds can exist which contain an atom of the following elements in an anomalous state of valence: N^{II}, N^{IV}, S^{I}, O^{I}, Si^{III}, Sn^{III}, Pb^{III}. We know now all kinds of free radicals.

[5] See full reviews: (a) Schmidlin, "Triphenylmethyl," Ferdinand Enke, 1914; (b) Walden, "Chemie der freien Radikale, S. Hirzel, 1924; (c) Gomberg, *Chemical Reviews*, I, 91–141 (1924).

INSTABILITY OF FREE RADICALS

It is not surprising that the existence of such free radicals has been overlooked for so long. They are among the least stable substances and would be destroyed under conditions which ordinarily prevail in synthetic work. Thus, for instance, the triarylmethyls unite with oxygen as greedily as does yellow phosphorus; they are very susceptible to reducing agents and to oxidizing agents; they unite instantly with iodine and bromine; they are sensitive even to traces of mineral acids; light affects them; even very gentle heat destroys many of them; they undergo spontaneously intermolecular oxidation and reduction; some show the tendency to unite with every possible solvent in which they are dissolved, and the different types of radicals unite with each other, as for instance $(C_6H_5)_2N \cdot CR_3$. But now, with the recognition of their extremely unstable and unsaturated character, the free radicals are readily prepared and their individual characteristics can be determined.

Obviously, the unsaturated character of the C, or N, or O, as the case may be, must impart to these odd molecules a great tendency to pair up among themselves and thus bring into play their unused, or unshared, valence electrons. And such indeed is the case. Seldom if ever is this tendency towards association entirely wanting. In by far the largest number of cases we have to remain satisfied with an equilibrium of this nature:

$$R_3C - CR_3 \rightleftharpoons R_3C + CR_3; \ R_2N - NR_2 \rightleftharpoons R_2N + NR_2, \text{ etc.}$$

This equilibrium has been found to shift in favor of the dissociation phenomenon with slight changes in the conditions of the experiment. Rise of temperature or increase of dilution augments the amount of dissociation of the dimolecular compound into the monomolecular free radicals. But, above all, the nature of the groups around the central atom exerts the greatest influence upon the degree of dissociation. So slight a change as the substitution of $(CH_3O \cdot C_6H_4)$ for (C_6H_5) increases enormously the extent of the dissociation of all radicals in the C and N series. In fact, three such groups on one carbon atom induce practically

100 per cent dissociation. There are other groups of similar influence, such as biphenyl, naphthyl, etc. It is still too early to make wide generalizations in this respect, we have to remain satisfied with a few meager empirical deductions. Hence, when we speak of free radicals, we always mean radical, in equilibrium with a certain amount of the undissociated completed molecules wherein the two radicals bring into exercise their full quota of valencies.

METHOD OF PREPARATION

The following equations will illustrate some of the typical methods which have been employed by various investigators for the preparation of these compounds. The reaction, in nearly all cases, must be carried out in strictly anhydrous solvents, and in absence of oxygen.

$$R_3C \cdot Cl + Ag \rightarrow R_3C - CR_3 \rightleftharpoons 2\,R_3C - \qquad \text{Triarylmethyl}$$
$$R_3C \cdot OH + 2\,H_2 \rightarrow R_3C - CR_3 \rightleftharpoons 2\,R_3C - \qquad \text{Triarylmethyl}$$
$$R_3C \cdot Na + ClCR_3 \rightarrow R_3C - CR_3 \rightleftharpoons 2\,R_3C - \qquad \text{Triarylmethyl}$$
$$R_2N \cdot H + O_2 \rightarrow R_2N - NR_2 \rightleftharpoons 2\,R_2N - \qquad \text{Diarylnitrogen}$$
$$ROH + O_2 \rightarrow RO - OR \rightleftharpoons 2\,RO - \qquad \text{Monoaryloxygen}$$
$$ClO_4Ag + I_2 \rightarrow O_3ClO - OClO_3 \rightleftharpoons 2\,O_3ClO - \qquad \text{Perchloryl}$$
$$R_4N \cdot Cl + \text{electrolysis} \rightarrow R_4N - \qquad \text{Tetra-alkylnitrogen}$$
$$PbCl_2 + RMgBr \rightarrow R_3Pb - PbR_3 \rightleftharpoons 2\,R_3Pb - \qquad \text{Triaryllead}$$
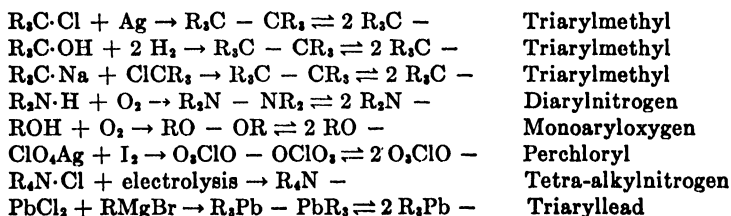
VALENCE OF ELEMENTS IN GROUPS I–III

A glance at the periodic table shows in what direction the experimental evidence has progressed. Starting with carbon in Group IV, practically all the elements in that group have been shown to act not only as quadrivalent or bivalent but also as trivalent. Then, one after another, representative elements from the groups to the right of carbon were also found to function with anomalous valence capacity. Nothing, however, of similar nature has yet been done with the elements to the left of the carbon group—almost one-half of the periodic table still remains, in this sense, uncharted sea. To quote from G. N. Lewis:[3] "It is a remarkable fact concerning the metals that we have so far discussed that when they form ions they give off simulta-

_____
[*] Reference 2, (b), p. 61.

neously all of the electrons of the outer shell. When Ca acts as an electrode in electrolysis, its atom never loses a single electron to form the ion Ca^+. If it does, this ion must be unstable and react immediately according to the equation, $2\ Ca^+ = Ca^{++} + Ca$ . . . Compounds of the type CaCl are unknown. Aluminium does not form the ions Al^+ and Al^{++}, nor are compounds known of the type AlCl and $AlCl_2$. In other words, when such a metal reacts it uses all of its valence electrons or none.''

It is therefore with no little trepidation that I undertake to report at this time some experimental evidence, meager as it still is, which seems to indicate that valence may become a variable function in some of these metals.

PROBABLE EXISTENCE OF MAGNESIUM-MONOHALIDE

It has been a well-known fact that when benzophenone, dissolved in perfectly dry ether, is treated with metallic sodium, reaction occurs without displacement of any hydrogen, and an intensely colored addition product is formed. When now this addition product is decomposed with water, there is formed, among other products, benzopinacol. Schlenk, in 1911, reinvestigated this reaction thoroughly and showed that practically all aromatic ketones make similar addition products with metallic sodium, potassium, and lithium. More recently, F. F. Blicke has made some additional observations in connection with this reaction. The reaction which occurs has been formulated as follows:

$$(C_6H_5)_2C = O + Na \rightarrow (C_6H_5)_2\overset{/}{C} - ONa \rightleftharpoons \overset{ONa}{(C_6H_5)_2\dot{C}}\overset{ONa}{-\dot{C}(C_6H_5)_2}$$

$$\downarrow HOH \qquad\qquad \downarrow HOH$$

$$(C_6H_5)_2C\Big\langle\overset{H}{\underset{OH}{}} + (C_6H_5)_2C\overset{-\ \overline{OH}}{\underset{-\ O\overline{H}}{}} \qquad (C_6H_5)_2\underset{HO}{C}-\underset{OH}{C}(C_6H_5)_2$$

Benzhydrol   Benzophenone   Benzopinacol
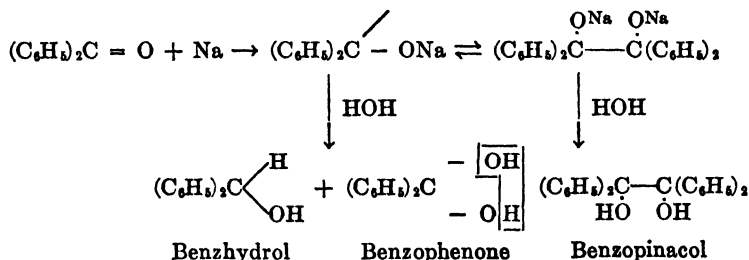
The strongly electro-positive character of metallic sodium, the tendency of the sodium atom to part with or share its single

valence electron, causes the establishment of the bond between the oxygen atom of the $C = O$ group and the sodium atom. As a consequence of this, the carbon atom becomes now trivalent, as it is in the triarylmethyls, and this free radical is undoubtedly in equilibrium with its more stable dimolecular form. If such a mixture is now hydrolyzed it must yield, among other products, some pinacol.

Recently, in connection with carrying out a Grignard reaction, an observation was made in our laboratory that metallic magnesium, which has been activated by means of iodine, reacts to some extent with benzophenone and small amounts of benzopinacol result, a phenomenon which has been noticed previously by others,[7] but for which no adequate explanation has been given. Jointly with Mr. W. E. Bachmann we have followed up this reaction and have obtained these results:

1. Magnesium powder as such, or even if amalgamated, does not react with benzophenone in ether or benzene, contrary to the statement in the literature.

2. Magnesium which had been activated by the addition of iodine or bromine does react with benzophenone. A gram atom of halogen for one mole of ketone gives in a short time practically 100 per cent yield of pinacol, even when the reaction is carried out at room temperature.

3. Magnesium iodide, in ether or benzene, combines with benzophenone in the proportion $MgI_2 \cdot 3(C_6H_5)_2CO$, but even on prolonged boiling of the mixture, no benzopinacol is formed.

4. When to a suspension of the above double compound in ether or benzene, powdered magnesium is added and the mixture is heated for a short time, reaction occurs and the pinacol salt is produced.

It is evident therefore that neither metallic magnesium alone, nor magnesium iodide alone, can accomplish the reduction of the ketone to the pinacol. It requires the simultaneous action of the two. What other unsaturated substance can there be formed in the reactions $Mg + I_2$, or $Mg + MgI_2$, that will function exactly as does metallic sodium, if it be not MgI? The one still

[7] (a) Schmidlin, *Ber.* **39**, 4202 (1906); (b) Schlenk and Thal, *Ber.* **46**, 2847 (1913).

unpaired valence electron in the magnesium atom of such a compound would correspond to the one valence electron in metallic monatomic sodium. Moreover, the MgI should have the added advantage over the sodium in that it is likely to be soluble, as MgI_2 is, in ether or benzene, and consequently the speed of our reaction with benzophenone should be faster than in the case of metallic sodium. Experiment verifies this—the reduction is quicker and the yield is ever so much better. We have tested out this reaction on some 10 aromatic ketones with surprisingly good yields of the corresponding pinacols.

It could hardly be expected that more than a minute amount of the MgI could be present at one time. The equilibrium in equation (a)

(a) $MgI_2 + Mg \rightleftharpoons 2\ MgI$; (b) $(C_6H_5)_2CO + MgI \rightarrow (C_6H_5)_2C - O - MgI$
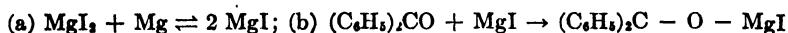
is no doubt preponderantly in favor of the left hand side of the equation. If, however, a ketone be present it will use up what little there may be present of this unsaturated active compound, (Equation (b)), and consequently more and more of magnesium monohalide will be produced. The restoration of the equilibrium proceeds quite rapidly. An appreciable amount of the ketone is reduced within the first few minutes.

Other interpretations of this unique reaction have suggested themselves, which are not so radical as the one given above, as for instance:

$$(C_6H_5)_2CO \xrightarrow{\ MgI_2\ } (C_6H_5)_2C\begin{matrix} \diagup OMgI \\ \diagdown I \end{matrix} \xrightarrow{\ Mg\ } (C_6H_5)_2C-OMgI + MgI_2$$
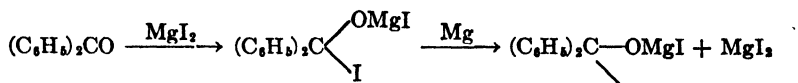
The compound with the trivalent carbon atom will then double up and upon hydrolysis pinacol will result. Or, with the co-ordination number for magnesium as 4, one may assume the possible formation of the coördinated compound as indicated in the equation below. The metallic magnesium would now remove the one atom of iodine in the secondary zone, and then, because of the increased affinity content of the magnesium atom

within the coördination complex, the compound $(C_6H_5)_2\overset{/}{C}OMgI$, the precursor of pinacol, would be formed:

$$[((C_6H_5)_2CO)_2 \cdot MgI]\ I + Mg \rightarrow 2(C_6H_5)_2CO + (C_6H_5)_2\overset{OMgI}{\overset{/}{C}}{-} + MgI_2$$
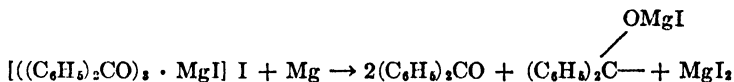
If either of the two suggested mechanisms be correct, then substitution of molecular silver for the metallic magnesium in the second step of the reaction should give better if not equally good results.   There is no reaction at all when metallic magnesium is replaced by metallic silver.

Our tentative hypothesis is, therefore, that MgI is the reducing substance in this reaction.   This new reducing agent has been tested out on aromatic aldehydes and esters, and the results indicate that its action, although more complicated than with ketones, is strictly parallel to that of metallic sodium.

It may be mentioned in this connection that a number of inter-metallic compounds have been described by Desch wherein Mg seems to function as univalent, such as $AlMg_3$, $SnMg_2$, and $AuMg_3$.[8]   May not the enhanced activity of amalgamated magnesium be due to the formation of some $HgMg_2$ and not merely to the fact that the magnesium in solution becomes more certainly monoatomic?

It might be added, that cadmium and zinc have given no indication of forming monohalides under conditions similar to those used with magnesium.   Berylium has not as yet been tested.

To sum up then, indications have been obtained that magnesium may be forced to function as univalent, in distinction from its normal bivalent state.   One may hope that similar methods of attack with other metals may yield more decisive results.

CONCLUSION

And so, on the one hand, the study of complex inorganic compounds has led to the conclusion that the valence of many

[8] Dean, "Theoretical Metallurgy," J. Wiley and Sons, p. 81 (1924).   For the very active alloy $PbMg_2$, see Ashcroft, Trans. Faraday Soc., 14, 276 (1919).

elements may become higher in number than their normal. On the other hand, the study of some complex organic compounds, of the so-called free radicals, proved that some elements may function with anomalous valences, lower than their normal. Concurrently, the physicist, through the momentous advances in the knowledge of atomic structure, has supplied the chemist with a logical concrete picture of the cause and the mechanism of valence manifestation. That picture predicates that, as a matter of course, valence for all but the inert elements must be variable and not fixed.

One may be pardoned, I hope, for attempting to view from this special angle some of the classic experiments of recent times. The determination, by the x-ray method of analysis, of the crystal structure of diamond by Bragg and of graphite by Hull, and by Debye, suggests that in diamond the carbon atom is quadrivalent, but that in graphite the fourth valence is weakened very much, even if not quite to extinction. Again, the positive-ray method of analysis indicates the production from CH_4 of univalent ions: C^+, $(CH)^+$, $(CH_2)^+$, which proves that the carbon atom in these is univalent, bivalent, and trivalent, respectively, assuming that the positive charge is acquired through loss of a valence electron. By the same method of analysis, according to J. J. Thompson, Hg functions, from Hg^I to Hg^{VIII}.[9] And when Millikan has stripped by explosive sparking some elements of all their valence electrons, the atoms pick these up again, not all at once, but one by one,—do not these results also indicate variability of valence capacity?

[9] F. W. Aston, "Isotopes," Edward Arnold & Co., p. 64, 72 (1922).

A BRIEF HISTORY OF THE INVESTIGATION OF INTERNAL PRESSURES

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Long ago Sir Isaac Newton perceived that the forces of cohesion and chemical affinity probably obey laws different from the simple law of gravitation (1).   At the time of writing the "Principia," however, his ideas on this subject were vague, as shown in the quotation:

> And now we might add something concerning a certain most subtle Spirit, which pervades and lies hid in all gross bodies; by the force and action of which Spirit, the particles of bodies mutually attract one another at near distances, and cohere, if contiguous; and electric bodies operate to greater distances, as well repelling as attracting the neighbouring corpuscles; . . . . But these are things that cannot be explain'd in few words, nor are we furnish'd with that sufficiency of experiments which is required to an accurate determination and demonstration of the laws by which this electric and elastic Spirit operates (2).

Newton evidently perceived that cohesive forces must fall off more rapidly with increasing distance than in the case of gravitation, whereas electrical attraction resembles gravitation more closely as regards its distance-effect.   The disastrous fire which consumed the results of so many years of Newton's work prevents us from knowing how searchingly Newton may have discussed these matters.   A hint of his line of thought, however, was published shortly before his death, indicating the important rôle which common sense played in his very penetrating ratiocination:

> The Parts of all homogeneal hard Bodies which fully touch one another, stick together very strongly.   And for explaining how this may be, some have invented hooked Atoms, which is begging the

Question; and others tell us that Bodies are glued together by rest, that is, by an occult Quality, or rather by nothing; and others, that they stick together by conspiring Motions, that is, by relative rest amongst themselves. I had rather infer from their Cohesion, that their Particles attract one another by some force, which in immediate Contact is exceeding strong, at small distances performs the chymical Operations above mention'd, and reaches not far from the Particles with any sensible Effect. . . . . There are therefore Agents in Nature able to make the Particles of Bodies stick together by very strong Attractions. And it is the Business of experimental Philosophy to find them out (3).

If, as Newton inferred, "the particles of bodies stick together by very strong attractions," these attractions must cause the atoms to exert great pressure upon one another. The internal cohesive and chemical pressures (that is to say, the pressures produced by cohesion and chemical affinity, respectively) thus exerted must be an essential characteristic of each form of matter. Furthermore (although Newton did not carry his argument so far), there must be resident in the atoms some resisting pressure or pressures to balance these; for otherwise the cooler parts of the universe would shrink to a collection of widely separated mathematical points of infinite density. It is the business of this paper to discuss the history of the study of these internal pressures, which have been also variously named "molecular pressures," "normal pressures," "intrinsic pressures," "Binnendrucke," "innere Krafte," etc.

The existence of internal pressure, important though it is, seems subsequently to have been ignored for thirty years, when the concept was revived by Segner (4) in 1750 to explain capillary action, a phenomenon long before discovered, probably by Leonardo da Vinci. Lack of experimental data doubtless contributed to this neglect,—which was continued for fifty years more, since not until 1804 did the question receive further attention. At that time Thomas Young (5), in the course of his epoch-making studies on capillarity, assumed that cohesive affinity is independent of distance "throughout the minute distance to which it extends;" but that it ceases entirely at the distance of 1×10^{-7}

mm. His argument is somewhat obscure, but he saw that one must assume a "repulsive" or distending tendency to withstand cohesion, and ascribed all the intimate variations of the effect to this latter tendency, which he assumed to diminish progressively with increasing distance. The nature of the "repulsive" force was not defined; as will be seen, it was often afterwards assumed to be purely thermal.

Laplace (6) in his almost synchronous comprehensive mathematical investigation of surface tension, also based his theory upon powerful cohesive forces. Nevertheless, as Lord Rayleigh pointed out,

In Laplace's theory . . . . no mention is made of repulsive forces, and it would appear at first as if the attractive forces were left to perform the impossible feat of balancing themselves. But in this theory there is introduced a pressure which is really the representative of the repulsive forces (7).

Laplace, perhaps quite independently, cast many of Young's ideas into mathematical form. He was probably the first to suggest that the work done by cohesive pressure should be considered as an integral involving some function of the changing attractive force.

After Laplace no other important addition to our knowledge of internal pressures seems to have been made before the contributions of Athanase Dupré in 1864. He was probably the first to point out that the expression $T\alpha/\beta$ (in which T is the absolute temperature, α the cubic coefficient of expansion and β that of compression) is a significant one (8) but he seems to have thought that this thermal pressure $T\alpha/\beta$ practically equals the total internal pressure. Dupré further saw clearly that cohesive pressure might account for heat of evaporation;—indeed there is no other reasonable explanation for this latter phenomenon. In attempting to compute thus the value of the internal pressure, he drew, however, an erroneous conclusion, namely, that the internal pressure multiplied by the atomic volume is equal to the heat rendered "latent" (9). Expressed mathematically, this gives

$\Pi = \dfrac{L}{V_A}$, in which Π is the cohesive internal pressure, L the atomic

heat of evaporation and V_A the atomic volume. The result is the same as it would be if the attracting pressure remained constant over a volume equal to the atomic volume and then suddenly ceased, although he reached the conclusion in different ways. As will be seen, his values were probably of the right order of magnitude, but the fundamental assumptions involved in his integration are questionable.

Hirn (10), whose thoughtful excursions into thermodynamics were often suggestive, was perhaps the first to consider (in 1865) the effect of cohesive pressure upon the gas-law; he introduced into the latter an additional pressure to account for the abnormally great contraction of imperfect gases on moderate compression, but made no attempt to relate this pressure mathematically to the cohesion of liquids.

The next important contribution to the subject of internal pressure was the well-known equation of J. D. van der Waals (11):

$$\left(p + \frac{a}{v^2} \right) (v - b) = RT$$

(1873) in which the idea of Hirn was amplified by making the assumption that the cohesive pressure varies inversely as the square of the volume. The basis upon which this assumption was made is somewhat obscure (12); perhaps it was partly pragmatic. Moreover, not only the basis, but also the later interpretation of the assumption is clouded. Although the square of the volume means ordinarily the sixth power of the distance, W. C. McC. Lewis has concluded that the attraction between the molecules varies inversely as the *fourth power* (13); whereas Mie (46) and Grüneisen (47) have concluded that the *cube* of the distance is involved. The relation is not necessarily the same when the molecules are very close together as when they are widely scattered. An adequate review of all the comments upon the questions raised by this classic equation would require a volume in itself.

The equation of van der Waals was undoubtedly a highly important step forward, but it cannot, for many reasons (including the assumption just mentioned) be considered as exact.

That it represents qualitatively the main influences at work, there can be little doubt.   On the other hand, the assumption that a is unchanging with temperature is questionable; and so is the assumption that the change of a with volume is simply exponential.   With regard to b the situation is even less promising.   Under very great pressures b is certainly not constant, and probably also it varies with temperature (14).   These considerations were at least partially recognized by van der Waals (15). Moreover, inferences drawn from the very extended gaseous state are not suitably applicable (in an unmodified form) to condensed phases without further evidence.   Hence van der Waals's equation, useful as it is, must be looked upon merely as an approximation.   The many later modifications of this equation are not sufficiently illuminating in relation to the internal pressures of solids and liquids to deserve mention here.   That of Keyes seems to be by far the best for gases (16).

The next important contribution was that by Maxwell (17), in connection with the theory of capillarity.   He perceived with Laplace that if cohesive attraction diminishes with distance, the work done by this attraction should be represented by an integral to which he gave the form

$$\int_f^\infty \phi\, f df$$

but not knowing the rate of decrease with distance, he was unable to give his equation definiteness.   His integral equation, like Laplace's, involved forces, not pressures, since f signifies distance.

Not long afterwards various other authors offered assumptions concerning the rate of decrease of cohesive force with distance. Pilling (18) advocated the inverse sixth power, and seven years afterwards Eddy (in 1883) (19) contented himself with a vaguer assumption,—that "some power of the distance" is concerned. In 1884 Harold Whiting (20) published his thesis upon a new theory of cohesion and maintained that the true function is the fourth power of the distance.   He admitted that this was an assumption.   Pearson (21), in 1888, brought forward an elaborate hydrodynamic atomic theory indicating that the exponent of the

distance-effect might be variable, according to circumstances, but never more than the fifth power. Five years later Richarz (22) attempted to prove by general theorems of mechanics that some of the propositions involved in the foregoing researches do not afford sufficient stability and must therefore be rejected. The experiments of Plateau, Quincke, Sohncke, Drude, Kelvin, Boltzmann (23) and others were designed to show the range of potent action, or the size of the molecules, rather than the rate of decrease of the diminished effect at a distance. Most of these investigators and, indeed, most later ones, have confined their attention to cohesion, and have left chemical affinity entirely out of consideration. The distending potential of atoms was usually neglected. Moreover, (as has been seen) often there was a tendency to deal with a force acting through a distance rather than with a pressure acting through a volume. Even in the case of capillarity, however, the well-known equation of Laplace, $(P = K + H(1/R_1 + 1/R_2)/2)$, shows that the surface-tension effect is merely a small difference between two great internal pressures, P and K, and that pressures therefore should enter into the integral equation (24a). The advantage of employing pressures instead of forces in the analysis is obvious in the work of Dupré, Hirn, and van der Waals.

The valuable and comprehensive work of Amagat on the physical effects of external pressure was rather experimental than theoretical, and concerned gases rather than liquids. Nevertheless, some of his data concerning the behavior of gases under very high pressures are pertinent (24b).

About forty years ago there was a marked reversion to the ideas of Dupré, already explained. Prominent among the theorists who embraced something like this point of view was Stefan (25) who advocated (among other doubtful hypotheses) an expression for the relation of latent heat to internal pressure essentially similar to Dupré's, except that the heat of evaporation was halved—because on an exposed plane surface a molecule may be supposed to be under the influence of half as many molecules as in the interior of the liquid. He seems to have left out of account the fact that when one molecule evaporates another must

rise to the surface to take its place (or, in other words, that the total shift is from complete immersion to vapor). Stefan's logic was accepted by many followers, including Ostwald and Walden, who made it the basis of a calculation of heats of evaporation (26). Harkins and Roberts have pointed out, on the basis of experimental results, that Stefan's principle is inconsistent with the change of surface tension with temperature (27). Rather recently Davies (28), and also W. C. McC. Lewis (29), used another expression, $\Pi = RT/(V - 0.27V_c)$, in which V_c is the critical volume. These investigations (to quote two examples) give values for the internal pressure of ether ranging from 1000 to 2000 atmospheres, and for that of benzene ranging from 1400 to 3000 atmospheres (75b).

A better theoretical method of attacking the problem had nevertheless been proposed (in 1888) only two years after Stefan's publication. G. Bakker felt, with Laplace and Maxwell, that an integral expression is necessary to represent the work involved, but suggested that this integral should involve the pressure-volume relation as the best indication of the work developed by cohesive attraction during change of volume (30). Thus he combined good points in the thought of Laplace and Dupré, although in many other respects his treatment was incomplete. He decided, like van der Waals, that the exponent of the volume to be used is 2, which leads to precisely Dupré's expression, although obtained in a more logical manner. In this way (as Traube and van Laar did also at a later date), he calculated heats of evaporation. None of these theorists considered the distending potential (except as indicated by the "constant" quantity b of Dupré, Hirn, Budde, and van der Waals) or the subsidiary thermal effects. Nine years after Bakker's contribution, Milner (31) proposed the inverse integral expression, which is, however, far less intelligibly applicable. Sutherland's rather speculative although interesting communications (1886 to 1893) bearing upon the question brought no definitive evidence, but deserve mention (32).

All of these investigations (except Isaac Newton's) concerned themselves with cohesive pressure alone. In other words, among

other omissions, they left wholly out of account the usually still greater pressures which must be caused by chemical affinity. Let us, then, turning back more than one hundred years, briefly glance at the few early incomplete researches which had taken chemical affinity into account.

Davy (33) in 1805 seems to have been the first to point out the great contraction which sometimes takes place when a solid compound is formed from solid elements; he inferred (in a footnote) that this contraction is greater, the greater the affinity. Sixty-five years later the same idea occurred to Müller-Erzbach (34), who showed that in many cases the contraction is greater the greater the heat of reaction, which leads to the same conclusion as Davy's, if heat of reaction is taken as representing approximately the free-energy change concerned. In the last decade of the nineteenth century the comparison was amplified by Traube (35). There were, however, many apparent exceptions to the general rule, and the idea received but a poor welcome from the physicochemical world. In the form then presented, the generalization was indeed both incomplete and inexact. None of these theorists distinguished adequately between the concomitant effects of chemical affinity and cohesion, and none considered the essential influence of the compressibilities of the factors in a reaction.

Furthermore, Traube complicated his presentation with several doubtful assumptions. Being an unqualified adherent to the van der Waals equation, he conceived of an incompressible atomic kernel and a "co-volume" ($v - b$, which, like the b of van der Waals, appears to me to be really rather a mathematical device than the index of a physical entity) and further complicated his thought by assumptions concerning "free-" and "bound-ether." These unnecessary assumptions tended not only to hide the real merit which his investigations possessed, but also to lead him astray.

Here the matter stood at the beginning of the present century. A number of physicists had interested themselves in the attracting pressure caused by cohesive forces and practically all of them had adopted van der Waals's assumption that this pressure varies

inversely as the square of the volume. A very few chemists had concerned themselves with the force of chemical affinity, but had made no attempt to represent mathematically its distance effect. All of the above mentioned later experimenters and theorists of both classes had omitted to take any account whatever of the inherent distending tendency in matter except as it is represented inelastically by van der Waals's "constant" *b*, which was not adequately interpreted. Van der Waals had assumed the atoms to be incompressible, and that their kinetic impact is instantaneous. There was, concomitantly, a general tendency (which was continued far into the present century) to assume that the only variable distending potential in matter is due to heat. Although van der Waals' equation received prompt and well deserved acclaim, the importance of the internal pressures of solids and liquids had produced so slight an impression on the minds of most chemists (or even of most physicists) that these internal pressures were scarcely mentioned in the textbooks of that time. Indeed even today they occupy a very unimportant place in most chemical treatises.

Nevertheless, Young's appreciation of the fact that the concept of a variable "repulsive" or distending potential inherent in matter is necessary in addition to the cohesive pressure, had not been wholly forgotten. In an interesting paper written thirty-five years ago (before many of the publications just mentioned) Lord Rayleigh (36) evidently felt the necessity of imagining some such pressure, but he did not essay to treat it mathematically, remarking:

The repulsive forces which constitute the machinery of this pressure are probably intimately associated with actual compression, and cannot advantageously be treated without enlarging the foundations of the theory.

He had much more to say about the attractive or cohesive internal pressure, which he called the "intrinsic" pressure; for example:

. . . . the progress of science has tended to confirm the views of Young and Laplace as to the existence of a powerful attraction operative at

short distances. Even in the theory of gases it is necessary, as van der Waals has shown, to appeal to such a force. . . . . Again, it would appear that it is in order to overcome this attraction that so much heat is required in the evaporation of liquids (37).

Further commenting on the question, Lord Rayleigh pointed out that the existence of great internal pressures is not only conceivable but is necessary, and that "all that we need to take into account is then covered by the ordinary idea of pressure."

Lord Rayleigh was dealing primarily not with the problem of internal pressure, but rather with that of surface tension, so that these remarks are incidental rather than basic. His pregnant suggestions might have served as the initial inspiration of my own work in this direction, if his paper had been known to me at the time. As regards the energy needed for evaporation, he accepted Dupré's equation, without analyzing its details, as a rough indication of internal cohesive pressure,—feeling with Dupré that the work of evaporation should be the mechanical equivalent of the heat involved. A concluding quotation from this paper may help to dispel a source of perplexity which sometimes influences commentors on the concepts involved in this discussion.

It may be objected that if the attraction and repulsion must be supposed to balance one another across any ideal plane of separation, there can be no sense or advantage in admitting the existence of either. This would certainly be true if the origin and law of action of the forces were similar, but such is not supposed to be the case. The inconclusiveness of the objection is readily illustrated. Consider the case of the earth, conceived to be at rest. The two halves into which it may be divided by an ideal plane do not upon the whole act upon one another; otherwise there could not be equilibrium. Nevertheless no one hesitates to say that the two halves attract one another under the law of gravitation. The force of the objection is sometimes directed against the pressure, denoted by K, which Laplace conceives to prevail in the interior of liquids and solids. How, it is asked, can there be a pressure, if the whole force vanishes? The best answer to this question may be found in asking another—Is there a pressure in the interior of the earth? (38).

A more comprehensive attempt to solve the problem was undertaken at the beginning of the present century. The subject was approached independently from the chemical side. In 1901, eleven years after the publication of Lord Rayleigh's thoughtful paper, the first of the present author's early papers on atomic compressibility was published. This and the immediately succeeding papers (39) brought evidence that the atomic volume is essentially dependent upon opposing pressures, and that the large incompressible kernel of the atom is a purely imaginary, (indeed an unnecessary and irrelevant) assumption. Thus the volume of the atom was assumed to be variable. For all theoretical as well as all practical purposes, it was taken to be the appropriate fraction of the actual volume of a solid or liquid element under given conditions,—that is to say, the "atomic volume" divided by Avogadro's number. Evidence was brought forward not only showing (in independent rediscovery of the outcome of Davy, Müller-Erzbach, and Traube) that cohesion and chemical affinity exert pressure and cause diminution in this volume (just as external pressure causes similar contraction); but also showing (for the first time) that the extent of this diminution of volume is determined also by the compressibility of each atomic sphere of influence under the particular conditions concerned. It was evident, from the considerable volume-changes occurring during the act of chemical combination and the very small compressibilities concerned, that the internal pressures produced by chemical affinity must be very great.

In short, the question was reduced simply to the idea that the balance of two opposing internal pressures, together with the external and thermal pressures, is the real key to the problem, although this conclusion was not expressed as clearly as it might have been. Many actual examples, of a partially quantitative type, were adduced to confirm the reasoning. Especially the parallelism of compressibilities (40) (determined for this purpose) and atomic volumes, together with the behavior of the alkali metals on combination, supported the argument. The origin of the idea was the conviction, based upon experiment, that the quantity b of van der Waals's equation is not constant (except

in an expanded gas at constant temperature, where it represents an abstraction which might be called the "collision volume" of the molecules) (41).

An important suggestion, made in the paper of 1901 (70, p. 8) was: that because the "atomic heat capacity" (i.e., the specific heat multiplied by the atomic weight) of a solid or liquid is partly due to the work involved in thermal expansion, it must be an approximate guide (in connection with the coefficient of expansion) to the amount of internal pressure present. Of course, as was there clearly indicated, not all of the heat needful to warm anything is available for work. Some of the heat must be used to provide added kinetic energy and the potential energy of temporary atomic displacement caused by vibration (42). But at any rate the heat and the work against the internal pressure (although not equal to one another) ought to be about proportional in different cases. Therefore the quotient of atomic heat capacity divided by the atomic expansion per degree $(C/V_A\alpha)$ ought to be an index of relative internal pressures (Π) in different substances. Mathematically, one might express the idea thus: $\Pi = fC/V_A\alpha$, where Π is the internal pressure, f an unknown fairly constant fraction, C the gram-atomic heat capacity, V_A the atomic volume, and α the coefficient of expansion. The inference was verified by examples and comparison with other properties. The original statement of the·qualification stated above (that f must be less than unity) was overlooked by Traube (44) and by W. C. McC. Lewis (75), the former applying it partially on his own account, and the latter rejecting entirely the suggestion. A fairer estimate of the situation was made by Carl Benedicks (43), who saw that if f is taken as 1/3, the tenets advanced in 1901 lead to the equation $\Pi = R/V_A\alpha$. This simple equation (in which, as in the previous one, Π = internal pressure, V_A = atomic value, and α = cubic coefficient of expansion while R is the gas constant) Benedicks offered only very tentatively as of distinct interest, but did not further apply numerically to the actual behavior of any form of matter. The probable significance and limitations of this equation will be discussed shortly, in connection with later work.

The American paper of 1901 seems to have stimulated Traube to calculate (in 1903) internal pressures and heats of evaporation, with results of a reasonable order of magnitude (44), by the equation of van der Waals.   Traube's results were inevitably vitiated, however, by incomplete logic and by the merely approximate character of van der Waals's equation, especially as applied to matter greatly compressed either by external or by internal pressure; they were appropriately criticized by Benedicks (43). A much more exhaustive prosecution of a somewhat similar line of thought has been recently offered by J. Berger and severely criticized by van Laar (45).

Almost at the same time, in 1903, Mie (46) published an important mathematical paper which contained, perhaps for the first time, an attempt to represent *mathematically* the effect of the distending or repulsive potential of matter already mentioned as having been studied qualitatively.   Mie was interested not so much in the magnitude of the internal pressures concerned, as in the calculation of the volume-changes caused by heat and by externally applied mechanical energy.   His equation was therefore an energy-equation, into which, however, he introduced the idea of integrating the pressure-volume effect of cohesive pressure after the manner of Bakker (30).   With the help of kinetic hypotheses, he analyzed the work involved in the volume-change of a monatomic metal, taking account of a distending as well as a compressing potential and assuming each to be a function of volume.   His equation of state took the form,

$$p v_F + A v_F^{-1} - \frac{\nu}{3} B v_F^{\left(\frac{-\nu}{3}\right)} = \frac{\nu + 2}{2} R \, \theta$$

In this equation, the first term represents the work due to external pressure, the second that due to cohesive pressure, the third that due to distending potential, and the fourth that due to heat.   The discussion of details would require too much space for the present brief history, especially because the result was not definitive.

Mie's excellent but incomplete theory was amplified and altered by E. Grüneisen (1911–1912), who has done valuable experi-

mental work. The latter also, in very elaborate mathematical papers (47), computed with success compressibilities and co-efficients of expansion by consideration of the work derived from four sources—external mechanical work, work done against cohesive pressure, work done by the distending potential, and work corresponding to heat. His equation of state (47b) took the form:

$$pv + n\frac{A}{v^n} - m\frac{B}{v^m} = \frac{(y+2)D_y - (x+2)\ D_xE}{6\ D}$$

which (like Mie's) involved the use of frequency. However, he immediately concealed the two most important terms in this expression (the second and third) by combining them in a single quantity, which represents their difference. Later he simplified the full equation of state (47c). Neither Mie nor Grüneisen attempted to compute the essential internal pressures concerned; neither of them employed the expression $T\alpha/\beta$ for thermal pressure; and neither looked upon the equilibrium which determines the bulk of a solid or liquid from the point of view of a balance of pressures. They dealt primarily with energy-equations, and rested their argument upon kinetic hypotheses. Nevertheless some of their suggestions are important, as has been said. In a contemporaneous paper, Debye (48) related the quantitative connection of energy and absolute temperature to the acoustical spectrum, deriving a well-known equation for specific heat at low temperatures, and in 1914 showed that neither Mie nor Grüneisen really made use of the two different terms for opposing internal pressures in their formulas for the potential energy, but that so far as their analysis goes, the only thing needed is that deviations from the simple Hooke Law should exist—the sense of these deviations being that more potential energy-change is involved in the diminution of the volume by the amount ΔV than in an increase by the same amount. In this very interesting lecture, Debye introduced the Quantum Hypothesis into the equation of condition of a solid, considering the latter as an asymmetric oscillator. He arrived deductively at Grüneisen's Rule, but did not attempt to compute internal pressures.

The contributions of Marcel Brillouin (who corroborated Debye) should also be mentioned, as well as those of Everdingen, H. A. Lorentz, Ornstein and Zernike, and Tresling. All of these authors (59) dealt largely with the meaning of the Grüneisen rule, considered from Debye's point of view.

More or less contemporaneously with these papers, a number of suggestions appeared concerning the rate of change with changing volume, which perhaps should be mentioned. In a long series of papers, Mills (50) assumed that the force of cohesion varies inversely as the square of the distance between the molecules—an assumption which might give cohesion a rôle in determining the motions of planets and satellites. Mills' assumption was supported by Kam (51), but controverted by Kleeman (52), (who advocated assuming the fourth to the sixth power of the distance) and by Mathews (53). Winther's (54), Tryer's (53) and Tammann's (56) papers should likewise be mentioned in this connection.

Later Wohl (57) adopted an equation somewhat similar to to Grüneisen's, but was inclined to ascribe the "repulsive" force primarily to rotation. Concerning the contributions of K. K. Järvinen (58) for which nothing more than approximate accuracy was claimed, it is only necessary to call attention to the fact that his results agree with the now discredited determinations of the compressibility of mercury made by Jamin. S. Pagliani (59) considering the internal molecular forces of solid substances and their relation with the elastic properties, devised a more complicated theory, subdividing the cohesive pressure into several components. The contributions of Drude and Nernst (60), Tammann (61), and Polowzow (62) concerning internal pressures of solutions deal with systems so complicated that any attempt to derive a simple law was foredoomed to failure at the present time. The complications involved are excellently set forth in recent papers by Baxter (63).

Van Laar, who for a number of years has published interesting mathematical papers dealing more or less with internal pressures, has recently summed up his conclusions in his book (64). He employed an integral equation, depending upon the equation of

van der Waals, and yielding a result very like that of Dupré, but somewhat modified by temperature terms. The well-known formulas for specific heat of Einstein (65) and of Nernst and Lindemann (66) (introducing half quanta, and preceding that of Debye) are connected with the interpretation of the phenomena under consideration, but need not be further discussed in this place. They are reviewed interestingly by Grüneisen.

Very recently important investigations have been made by several physicists, attacking the subject from an entirely different standpoint, and founding the argument upon hypotheses concerning the electronic nature of the atom. The three chief investigators in this direction have been, F. Haber, Sir J. J. Thomson, and Max Born (67). These contributions are stimulating and suggestive; but they, like Mie's and Grüneisen's, possess the inevitable disadvantage which always inheres in any deductive attempt to predict the facts when only hypothetical premises are employed. Both Thomson and Born came to the conclusion that compressibility is a function of atomic or molecular volume alone. That molecular volume is indeed one of the essential premises in the argument had been shown long before in the first comprehensive research on the compressibilities of the elements (68); but this early research showed also that molecular volume is not the only variable to be taken into account. Hence neither of these more recent suggestive discussions could be expected to yield more than approximate results. That the outcome should be as satisfactory as it was is a cause for congratulation.

Some of those who advocate the electronic explanation believe that both the repelling and attracting forces are due to the same cause, and that the condition of equilibrium is one not of opposition but rather of a kind of neutrality. This view involves the assumption that Coulomb's Law is greatly modified at short range (perhaps by quantum forces). A simple definitive explanation along this line seems far to seek.

Is it indeed possible to gain exact quantitative knowledge, from any source, concerning a problem so recondite, dealing with concealed pressures so mutually entangled and so far removed

from the range of actual experiment?   Recently (in 1916) Jeans has written: "The effect of the forces of cohesion is too complex for an exact mathematical treatment to be possible" (69); and this feeling has been at times shared by others, including the present author.   Nevertheless, the question is so fundamentally important that even an incomplete answer is vastly better than none.

The attracting and repelling tendencies which determine the behavior of solids and liquids are different in many ways from any other forces in nature.   It would appear, then, that for their understanding and evaluation one must pursue an inductive quest, relying in phenomenological fashion upon the actual effects which are produced by the powerful influences involved. That is to say: the basis for the determination of internal pressures would seem to be found in the actual behavior of solids and liquids under the action of thermal and mechanical energy. This proposition was indeed implicitly recognized by many of the earlier authors already quoted.   That density, coefficient of expansion, specific heat, heat of evaporation, and compressibility, as well as many other properties of matter having to do with physical and chemical condition, must be dependent upon internal pressure, was especially emphasized in 1901 (70).

At that time, and in the immediately following years (71), it was shown that in all probability, as a general rule, the greater the coefficient of expansion, the less the internal pressure; again, the greater the compressibility, the less the internal pressure; and yet again, the greater the decrease of compressibility with increasing external pressure, the less the internal pressure. Nevertheless data were lacking for numerical calculations leading to an exact quantitative theory.

In 1922, however, the remarkable work of Bridgman on the compressibility of thirty metals to 12,000 atmospheres' pressure, was published (72).   These results, which had been kindly communicated to me by Professor Bridgman some months before publication, promised at last a means of penetrating more deeply into the mystery.   Bridgman's thermodynamic treatment of them was primarily concerned only with external pressures, and he made no attempt to compute from them the much greater

internal pressures involved. Nevertheless they furnished an exceptionally good basis for inference concerning these internal pressures, especially because many of the metals studied were isotropic and therefore presented a simple and more intelligible basis of analysis of the problem than is possible where more than one intensity of internal cohesive pressure is present at the same time in the same substance.

The opportunity was immediately grasped, and the first hopeful outcome was the discovery of a very simple hyperbolic interpolation equation (73) which represents with great precision the effect of pressure and temperature on the volume of heavy metals such as gold and silver. This equation took the form

$$(p + P) \ (v - B_1) = k_1 + cT$$

In it p is the external pressure applied by a pump and measured by a gauge; P represents (but is not necessarily exactly equal to) the hidden internal cohesive pressure which holds the metal together; v is the volume; B_1, k_1, and c are constants; and T is the absolute temperature. The agreement of this equation with the actual results for many heavy metals was within the limit of error of experiment, and an approximate agreement existed even with the more compressible alkali metals. Somewhat similar equations had previously been used over short ranges for organic substances by Tumlirz and Tammann (74). Their treatment of temperature was, however, inadequate and not illuminating, and their equations were merely first approximations as regards the behavior of the complex substances concerned.

The above stated equation is an energy-equation, analogous to that of van der Waals,—although the B_1 value is smaller in magnitude than the b of the latter's treatment. But we are concerned primarily with pressures, and not with quantities of energy; because the equilibrium which exists in a solid or liquid at ordinary temperatures must be really a balance of pressures. Therefore this expression was reduced to an equation of pressures by dividing it through by the volume $(v - B_1)$ as follows:

$$p + P = \frac{k}{v - B_1} + \frac{cT}{v - B_1}$$

The transformed equation still has four terms, but now each represents a pressure. The first term, p, is simply the external pressure; the second represents pressure caused by *cohesion*, the third represents that portion of the *distending*, "repulsive" or repelling tendency which is independent of heat, and the last, the remainder of the distending pressure, caused by heat. The *compressing* tendencies are in the left-hand member, and the *distending* tendencies in the right.

Here we have experimental evidence that a distending potential, independent of heat, is an important influence in the balance of pressures. It is indeed, except in very volatile substances, much greater than the thermal pressure. The latter (the fourth term in the immediately preceding equation) was shown, by a process of reasoning too extended for exposition here, to be equal to the absolute temperature multiplied by the coefficient of expansion and divided by the compressibility, $(T\alpha/\beta)$—one of Dupré's old expressions. Thermodynamically it is a valid quantity, equal to $-T(\partial p/\partial T)_v$. This quantity represents only one of the four opposing pressures, namely, that due to thermal energy. In the case of very volatile substances, $T\alpha/\beta$ is indeed not very much less than the total distending pressure, but with non-volatile substances this thermal pressure is only a small part of the total tendency which resists compression. If the sole distending tendency in matter were this one, due to heat, (14b, page 626) matter would shrink to zero volume at the absolute zero of temperature;—for example, Kamerlingh Onnes' apparatus for liquefying helium would have been reduced to very small dimensions before the liquid could have been obtained.

An obvious difficulty in the preceding equation is the assumption of the constancy of the quantity representing cohesive pressure, P, whereas really this pressure must increase very rapidly with decreasing volume. If this latter conclusion is true, in order that the equation may (as it does) represent the facts, the expression for the distending tendency $k/(v - B_1)$ must also increase with decreasing volume. Therefore a different method of stating the second and third terms is needful.

In its most general form the equation of state of any condensed phase composed of a single species of monatomic molecules under definite conditions may evidently be expressed by the simple equation[1]

$$p + \Pi = \Pi_\rho + T\alpha/\beta$$

in which Π depicts the true internal cohesive pressure (represented roughly by P in the preceding equation) and Π_ρ depicts the true internal repelling or distending pressure independent of heat. But because each of these internal pressures must be assumed to change with changing volume, as has been said, the following amplification (73b) presents a much better picture of the situation:

$$p + \Pi_o \left(\frac{v_o}{v_1}\right)^m = \Pi_{\rho_o} \left(\frac{v_o}{v_1}\right)^n + \frac{T\alpha}{\beta}$$

This equation (in which Π_o and Π_{ρ_o} correspond to the volume v_o) appears to be rather complex, but the ideas concerned are really simple enough. It is easy to see that (at ordinary temperatures) since Π_o is larger than Π_{ρ_o}, whereas n is larger than m, the difference between the actual changes in the second and third terms with moderately changing volume might very well be equal to the increase in p—a supposition which would explain the approximate validity of the simpler hyperbolic equation already given. So far as present analysis can show, m is usually not far from 2, being often about 1.7. The exponent n is much larger than m; if it were not, all matter would collapse under slight external pressure.

The above equation combines the static and the dynamic points of view by virtue of its use of the dimension of pressure as the key to the situation—for pressure may be exerted either by a steady push (as in the cases of p, Π, and Π_ρ) or by a succession of kinetic impulses (as in the case of $T\alpha/\beta$). The impulsive pressure

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[1] This equation represents mathematically the basic idea in the author's work since 1901. The idea was perhaps somewhat vaguely expressed at first, but it had assumed very definite form shortly afterwards (71, pp. 2435-2437). See also 73a, p. 425, and the paper written in collaboration with E. Saerens (67).

produced by heat must cause an oscillation determined in its range by the rate of increase and falling off of the two great static opposing internal pressures. It appears to act in the whole volume occupied by the atom. Obviously when any given thermal impulse is great enough to over-balance the above-mentioned equilibrium, the atom (or molecule) carrying the impulse must be set free,—i.e., evaporate. The situation appears to be well adapted to furnish a suitable mechanism for the physical and chemical reactions necessary for constructing a workable universe and a physical basis of life.

The new equation for monatomic elementary substances, thus independently developed, seems to make possible the weaving together into a consistent fabric many of the diverse threads which other investigators had gradually accumulated. It contains, like the equations of Mie and Grüneisen, a term for each of the four separate tendencies affecting the volume of a condensed phase. It gives prominence to the third term depicting the non-thermal distending or repelling tendency in matter, which has been so often neglected. In keeping the second and third terms separate from one another it emphasizes their essentially opposite nature. It installs as the fourth term a quantity which seems to express the true thermodynamic magnitude of thermal pressure, $T\alpha/\beta$ (or $-T\,(\frac{\partial p}{\partial T})_v$). It shows, on the other hand, that this last term does not represent (as Dupré (8) and others (75) appear to have thought) the whole of the distending tendency in matter. Finally it assigns to the exponents of the two volume ratios symbols (m and n) which are independent of the gas-equation of van der Waals, and which challenge evaluation on the basis of the behavior of the condensed phase itself under mechanical and thermal pressure.

The most important distinguishing feature of the new equation is the treatment of the two opposing pressures Π and Π_ρ as separate entities, operating presumably by different mechanisms. This feature is probably that least acceptable to many physicists, who may prefer dealing merely with the difference ($\Pi - \Pi_\rho$), after the manner of Grüneisen, Kleeman (52) or Eucken (83),

or else prefer maintaining (as has been said) that equilibrium is a neutral point in an hypothetical electrical system governed by anomalous quantum forces. But if as it appears, the exponent m is the same (somewhat less than 2) with many substances (81, p. 734) and since, furthermore, both thermal expansibility and latent heat of evaporation as well as chemical heat probably point toward pressures of the full magnitude of Π, does not the individual quantity Π acquire real significance? And is not then the use of the mere difference between Π and Π an evasion of the issue? Moreover, the dissociation of the treatment of these two tendencies has much to recommend it, not merely for mathematical convenience, but also because of analogy with other physical phenomena. In general, when in a series of observations a maximum or minimum exists, strong evidence is afforded that two different mechanisms are at work. Such an inflection appears in the relations of the internal forces to distance,—an inflection too marked to be accounted for without the assumption of a concrete distending tendency other than heat. The fact that Π and Π_ρ must ultimately be referred to forces does not invalidate the treatment of these tendencies as pressures concomitantly with external and thermal pressures.

The four unknown quantities Π_o, Π_{ρ_o}, m, and n could theoretically be determined by four equations, involving different relative volumes and pressures, and representing the actual behavior of an isotropic element, provided that m and n were unchanging in value. But this last proviso is not necessarily fulfilled, although for a comparatively small range of volume definite values may be assumed without serious error. The range of volume experimentally available with comparatively incompressible substances is of necessity small.

A more convenient method of advance was found in the study of a series of "synthetic" pressure-volume curves, built up on definitely assumed internal pressures and exponents, and in the comparison of these with the pressure-volume curves actually exhibited by isotropic substances. This study can not be detailed here. It sufficed to show that the Π_o values are of the order of magnitude of the P in the hyperbolic interpolation

equation; and that when m is 2 and n is 7, the two quantities P and Π are nearly equal. Increasing n increases P and diminishing n diminishes P in relation to Π. From these considerations also, the initial compressibility β_o at the absolute zero (where $T\alpha/\beta$ is 0) was found to be $\beta_o = 1/(\Pi_o (n - m))$—an important relation which may be used for the direct computation of Π_o when the difference $(m - n)$ is certainly known, or of $(m - n)$ where Π_o is known (77, p. 733).

These considerations make possible the approximate determination of the internal pressures in the isotropic metals, depending upon the experimental results of Bridgman. It appears that Π_o is, for example in the case of silver, about 160,000 megabars. The amount of calculation involved is great and has not yet been applied to many other cases, but there seems little doubt that the outcome is reasonable and that the equations just given afford an adequate picture of the behavior of isotropic solids. Very recently J. E. Jones, from a study of solid argon (76) has confirmed in a remarkable manner not only the point of view, but also some of the quantitative aspects of the development.

This outcome is supported in rather striking fashion by an entirely different method of approach depending upon facts of a different kind, namely, by the study of the coefficient of expansion, a property like compressibility concerned with the great internal pressures existing in solids and liquids. That the coefficient of expansion is primarily dependent upon internal pressure was perhaps first emphasized (70) in 1901 as has been already indicated above.

The coefficient of expansion of a solid or liquid is always much less than that of a perfect gas. The probable reason for this difference may well be as follows: In solids and liquids the pressure produced by heat must be only a small part of the total pressures concerned (as is shown by the foregoing equations) whereas in the case of a perfect gas the energy of heat must cause the whole distending effect. Is it not then reasonable to draw an inference concerning the magnitude of this greater pressure from the comparison of the two coefficients of expansion? The

coefficient of expansion of silver at 20° is about one sixty-first of that of a perfect gas. The kinetic energy involved is generally believed to be identical in the two cases. May it not then be that the total pressure involved in the expansion of silver is sixty-one times that which a gram-atom of a perfect gas would exert in the same volume? If this is the case in general, the internal pressure of a metal at 20°, for example, would be

$$\Pi = \frac{RT}{V_A} \frac{0.00341}{\alpha_s} = \frac{R}{V_A \alpha_s}$$

This expression makes precisely the above comparison (73b). In it Π, as before, signifies cohesive internal pressure; T, absolute temperature; R, the gas-constant; $0.00341 = 1/T = \alpha_g$ (the coefficient of expansion of a gas) α_s the coefficient of expansion of the solid; and V_A the atomic volume. The above equation is identical with that tentatively suggested but not applied by Benedicks (43) in entirely different fashion upon the basis of an earlier proposition (70).

From the point of view here adopted, this equation is, however, only a first approximation. The expansion of a perfect gas is measured under constant pressure, whereas the expansion of a solid is measured under a slightly changing *total* pressure (although under a constant *external* pressure); for as the solid expands the internal pressure Π must diminish; and even if the external pressure is kept constant, the total pressure against which the energy of heat is acting must be diminished during the expansion. In order to be entirely consistent, then, α should here signify the coefficient of expansion when the total pressure $(p + \Pi + \Delta p)$ is kept constant (Δp being the slight change in p necessary to replace the small loss of Π due to the increased volume on heating (77). The correction is, however, a small one; it leads to values of Π slightly higher than the uncorrected values. Its exact amount can not be precisely determined until the constancy of Π in constant volume with changing temperature has been proved (78).

At very low temperatures the equation needs modification for the little understood reason which causes the failure of Dulong

and Petit's Law. The "Grüneisen Rule" that for a given substance α is approximately proportional to C (the molecular heat capacity), indicates this parallelism. Evidently a more correct expression is that advocated (and expressed in words, but not in symbols) in 1901 (70), namely,

$$\Pi = f\ (C/V_A\alpha)$$

At ordinary temperatures $C = 3R$ approximately, and $f = 1/3$. At very low temperatures $C/3$ is no longer equal to R. Further discussion of this aspect of the matter must be postponed.

However this may be, the equation

$$\Pi + \Delta\Pi + p = R/V_A\alpha$$

gives at ordinary temperatures a good means of predicting rather closely the effect of pressure on the coefficient of expansion and compressibility, as will be shown in a subsequent paper. For example, the coefficient of expansion of mercury under 3,000 megabars pressure (p') is computed to be $\alpha_p' = R/14.75$ (31,000 + 515 + 3,000) = 0.000163, whereas Bridgman's experimental value is 0.000164, both being referred to V_A at 0°C. The value $\Delta\Pi = 515$ is calculated on the assumption that $m = 1.7$; it represents here the increase of cohesive pressure due to the diminished volume caused by the external pressure, p' = 3,000.

Taking everything into consideration, it accordingly appears that

$$\Pi = C/3V_A\alpha;\ \ or\ \ R/V_A\alpha$$

(for ordinary temperatures) may therefore be accepted as a promising, if not rigorous, means of computing internal pressures, which gives results somewhat, but not much, too low. Accordingly, table 1 is given to show the approximate internal pressures in a number of isotropic* metals compared in this way, R being 83.16 megadyne-cm./°C.

These pressures are very large, but not unreasonably so. That at least they are not far from the right order of relative magnitude

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* "Isotropic" is used here in its original sense and not as synonymous with "amorphous."

is likely. Moreover the fact that they are about equal to values computed from the pressure-volume curves alone (that is to say, from compressibility), strongly supports their approximate accuracy. If volatile liquids possess internal pressures of the order of a thousand or more atmospheres, as is generally conceded, the magnitude of these values for metals is not excessive. They are not far from the values calculated by Traube (44) from the equation of van der Waals. Griffith has found experimentally

TABLE 1

Approximate internal pressures of isotropic metals based on atomic volumes and cubic coefficients of expansion (at 20°C.)

METAL	COEFFICIENT OF EXPANSION	ATOMIC VOLUME	INTERNAL PRESSURE
Caesium...............................	300	71	4,000
Potassium.............................	245	45.4	7,500
Sodium................................	215	23.7	16,300
Mercury...............................	181	14.8	31,000
Lead..................................	85	18.3	53,000
Calcium...............................	50	25.3	66,000
Magnesium.............................	74	13.3	85,000
Aluminum..............................	65.5	10.1	126,000
Silver................................	55.6	10.3	145,000
Gold..................................	43.2	10.2	189,000
Copper................................	48.4	7.1	242,000
Palladium.............................	34	8.77	279,000
Tantalum..............................	24	10.9	315,000
Nickel................................	38	6.7	327,000
Cobalt................................	37	6.85	329,000
Iron..................................	34	7.1	345,000
Platinum..............................	26.4	9.1	347,000
Tungsten..............................	13.7	9.6	632,000

values of the same order of magnitude from the tensile strength of glass fibers (79).

The heat of evaporation of mercury affords support for the corresponding value given in the above table, and therefore indirectly for the other values. When the attracting and repelling pressures and *m* and *n* are known, one should be able to compute from the second equation on page 334 the work required for pulling the atoms apart—in other words, for evaporat-

ing the substance. This work (when corrections for such small concomitant effects as external work and heat expelled because of change of heat capacity are made) should be equal to the heat of evaporation. The difference between the pressure-
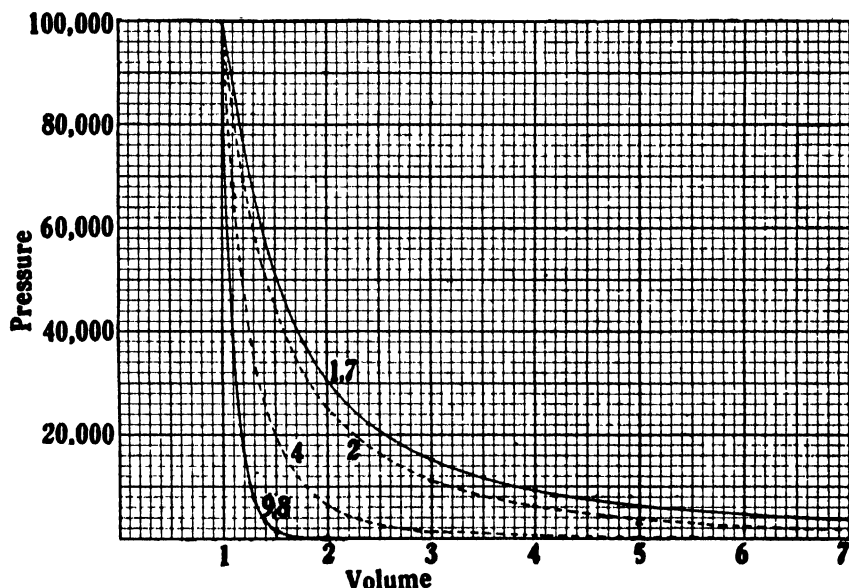
FIG. 1. THE WORK OF EVAPORATION DONE AGAINST COHESIVE PRESSURE

Multiples of the atomic volume are plotted as abscissae (abscissa 1 corresponding to the atomic volume of the condensed material). Pressures in megabars are plotted as ordinates. The difference between any two integrals, that is to say, the *area* between any upper curve (representing the decrease of cohesive pressure with increasing volume) and any curve below it (representing the decrease of internal repelling pressure with decreasing volume) represents the work required to separate molecules from a condensed condition to a distended vapor. This diagram holds precisely only at the absolute zero, thermal pressure not being included in it. It assumes that the internal pressure in the liquid or solid is 100,000 atmospheres; for any other internal pressure, the appropriate fraction or multiple of the differences between integrals gives the corresponding work.

volume integrals of the second and third terms of this equation constitute the chief part of the energy in question. This difference is represented by the *area* between any two curves in the diagram (fig. 1) in which the numbers on the face of the diagram near the curves represent the exponents of the volume ratio.

On the other hand the equation of Dupré is represented by the rectangle at the left of ordinate 1. Evidently, for any reasonable values for n or m, the area between the curves will be of about the same order of magnitude as Dupré's expression. In the case of mercury m has been estimated as 1.7 and n as 9.8. The internal pressure of liquid mercury is probably somewhat over 30,000 megabars. Therefore the area as depicted on this diagram (in which the internal pressure is chosen arbitrarily as 100,000 atmospheres) will be about three times too great, to correspond to mercury. Dividing the area (as found exactly by integration) between the continuous curves 1.7 and 9.8 (up to infinite volume) by 3, one should obtain a result for a quantity of work about equal to the heat of evaporation. This is indeed the case (73b, p. 1433; also 81, p. 735).

These confirmations, from so many sides, give the theory considerable probability, and warrant its use at least as a working hypothesis.

All of the immediately preceding discussion applies in an unmodified shape only to isotropic or rather *monatomic* elements. When chemical affinity is present, modification of the treatment is needful.

As has been said, few of the many investigators upon the subject have included chemical affinity in their consideration. Yet this force is no less important than cohesion, which in many respects it resembles (84). Like cohesion, chemical affinity must produce very great pressures which fall off very rapidly as the attracting atoms recede from one another (2, 80); and like cohesion, chemical affinity may in many cases be overcome by the energy of heat. The similarity is great enough to warrant the application of the foregoing principles, inferred from one set of phenomena, to the more complicated situation presented by the other. New difficulties arise in the treatment, due not only to the fact that in a compound at least two different elements are present at the same time, but also to the probability that each chemically combined atom is subjected to different intensities of pressure on different portions of its surface. Nevertheless, the venture

seemed to be worth making, since even a vague outcome would be better than none.

Accordingly, within a few months (81) the method of treatment outlined in the immediately foregoing pages has been expanded to include the pressures produced by chemical affinity. The outcome shows that the same principles which apply to cohesion may apply also to chemical affinity, bearing in mind the fact that chemical affinity acts most strongly on the portions of the atoms in closest juxtaposition and does not envelop each atom equably over its whole surface after the manner of cohesion in an isotropic element. Just as the heat of evaporation may be accounted for chiefly by the work involved in separating atoms under the influence of the changing balance of pressures, so the heat of chemical combination may be accounted for chiefly by the work done by the more considerable one-sided pressures usually produced by chemical affinity. This verifies a much earlier prediction based upon the relation of volume-change to heat of reaction (82). Even the recent discussion was inevitably tentative, because the portion of the atom involved by the one-sided action of chemical affinity is not easily defined. Nevertheless it was possible to show that the amount of work which may be done by the chemical union of two atoms is of the order of magnitude of the heat evolved. Of course, for completeness in this case, as in the other, correction must be made (on the basis of the so-called third law of thermodynamics) for the change of heat capacity during the reaction.

The equations presented by the most recent investigations thus seem not only to explain the pressure-volume-temperature behavior of solids, and liquids, but also to give a roughly quantitative picture of the *raison d'être* of heat of evaporation and of chemical reaction. Further investigation now in progress must proceed slowly, partly because of the time needed for calculation, and partly for the reason which halted Newton at a much less advanced state of the inquiry, namely, the lack of "a sufficiency of experiments." But nevertheless, although incomplete, the knowledge already gained, step by step, through the successive

advances of many investigators, gives a conceivable and rational picture of the action of the mechanism whereby solids and liquids (forming the framework of the universe) maintain their equilibrium. What the basic causes of the great pressures indicated may be, cannot yet be definitely decided. Perhaps these causes may be entirely electronic, but of course the demonstration of such a cause can be complete only when it is conclusively shown that electrical attractions and repulsions may really be capable of producing the very great but balanced pressures which are indicated by the actual behavior of condensed matter.

Incomplete although our knowledge of internal pressures may still be, one feels that at least something has been accomplished toward the fulfilment of Newton's parting injunction: "It is the Business of experimental Philosophy to find them out."

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THE RADII OF ATOMS AND IONS

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ATOMIC SHAPES AND RADII

A few years ago when atoms were thought of as being tiny solid baseballs, the term *radius* had a very definite meaning. In these days the picture of an atom is much more complex. We are given our choice of a static atom founded mainly on data obtained from solids and liquids, or of a Bohr atom founded mainly on data obtained from the spectra of elements in the gaseous state. In terms of the static atom picture, the word "radius" would be applicable to a circumscribed sphere passing through all the electrons in the outmost shell. In the Bohr picture, we might apply the word "radius" to the distance from the nucleus to the most distant part of the largest electronic orbit. Neither of these "radii" are quite consistent with the data of crystallography as determined by the diffraction of x-rays.

The atoms of an element pack together in a crystal as though they were solid objects in contact with each other. If models are made of the crystals of the elements, using balls to represent the atoms, it is found in general that each ball is surrounded by others which are symmetrically placed around it and which lie in direct contact with it. Within the limits set by the compressibility of the element and its thermal expansion, each atom seems to occupy a definite domain which, under ordinary conditions, may not be entered by any other atom. Such a state of affairs is hardly to be expected from the current pictures of atomic structure, yet such are the experimental facts of X-ray crystallography. It is as though each atom were completely surrounded by a "field of force" which set it apart from its neighbors. The region occupied by this "field of force" is the crystallographer's "atomic domain." It is with the shapes

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and sizes of these domains that the crystallographer has to do, for they give him a definite mechanistic picture of how the atoms of the elements may be expected to act under various conditions. From the crystallographic point of view, these shapes and sizes are the effective shapes and dimensions of the atoms themselves.

Many elements crystallize in the face-centered cubic lattice (see fig. 1). Since a face-centered cube is one of the two alternative closest packings for spheres, it is assumed that such atoms have a spherical shape (1) (2), i.e., that their atomic domain is a sphere. Such elements are, Cu, Ag, Au, Ca, Al, Ce, Pb, Th, gamma Fe, Co, Ni, Rh, Pd, Ir, and Pt. It will be noticed that
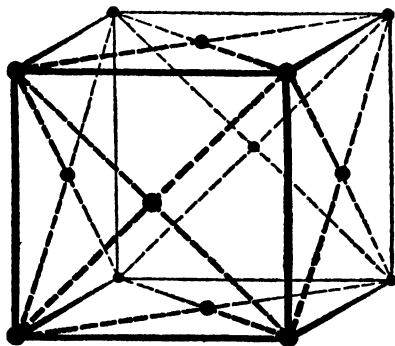
FIG. 1. FACE CENTERED CUBIC LATTICE

all the most ductile metals and all the best conductors of electricity are included in this group (2) (3). Each atom is surrounded by six others, symmetrically placed around it and apparently in contact with it. A line joining the center of any atom with the center of any one of the six which touch it will lie along the face diagonal of a unit-cube of the crystal lattice. The distance between the two centers is the distance of closest approach of the atoms. Half of this distance is therefore the radius of the atomic domain, or, as it is more often called, the "packing radius" of the atom; it is $\frac{1}{4}\sqrt{2}$ times the edge of the unit-cube of the crystal. The higher the purity of the metal used in the experiment, the more accurate is the measurement of

the edge of the unit-cube.   The radii of metals having spherical atoms are given in table 1, using data from metals of the highest purity obtainable.

The other alternative closest packing for spheres is the triangular close-packed lattice (see fig. 2) when the axial ratio is 1.633.   Co and Ce are the only elements known which are able to crystallize in this form with an axial ratio of exactly 1.633. Both of these elements are also found with the face-centered cubic structure.   The other elements which crystallize in the triangular close-packed lattice have axial ratios ranging from 1.58 to 1.89.   It is therefore assumed that the atoms of Co

TABLE 1

Radii of spherical atoms

ELEMENT	PURITY	RADIUS	ELEMENT	PURITY	RADIUS
(1) Cu...	99.99%	1.276×10^{-8} cm.	(3) γ Fe.	?	1.27×10^{-8} cm.
(1) Ag....	99.999	1.442	(2) Co...	Electrolytic	1.257
(1) Au....	99.999	1.437	(1) Ni...	99.55	1.237
			(2) Rh..	?	1.350
(2) Ca....	?	1.97	(2) Pd...	?	1.397
			(4) Ir...	?	1.352
(1) Al....	99.97	1.430	(1) Pt...	99.995	1.383
			(1)	Davey	
(2) Ce....	?	1.82	(2)	Hull	
(1) Pb....	99.96	1.740	(3)	Westgren	
(1) Th...	?	1.77	(4)	Wykoff	

and Ce are spherical and that the other atoms which crystallize with this type of structure are spheroidal (2).   Since the axial ratios of Be, Mg, Ti, Zr, Ru, and Os are less than 1.633, their atoms are considered to be oblate spheroids.   Zn and Cd are assumed to be prolate spheroids.   All these atoms are therefore given two radii which are half the major and minor axes of the spheroid.[1]

The equatorial radius is half the distance of closest approach in the direction of the hexagonal (X and Y) axes of the crystal.

[1] Hull (2) lists, instead, the two distances of closest approach of atoms.   One of these is the same as the equatorial radius.   The other is intermediate between this and the axial radius.

The other, which we will call the axial radius, is the radius of the spheroid along the orthogonal (Z) axis of the crystal. Radii of this sort for the spheroidal atoms are listed in table 2.
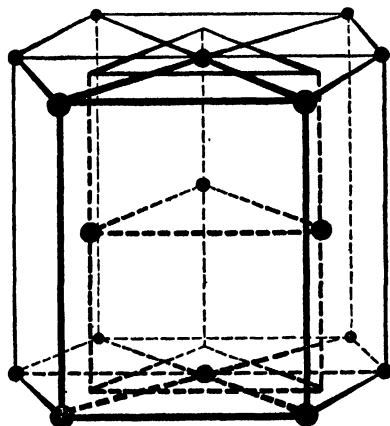
FIG. 2. TRIANGULAR CLOSE-PACKED LATTICE

TABLE 2
Radii of spheroidal atoms

ELEMENT	EQUATORIAL RADIUS	AXIAL RADIUS	SOURCE OF DATA
Be..	1.141	1.106	McKeehan
Mg..	1.597	1.593	Meier
Zn..	1.329	1.515	Pierce, Anderson and Van Dyck
Cd..	1.480	1 714	Hull
Ti..	1.478	1.439	Patterson
Zr..	1.61	1.57	Hull
Ru..	1.343	1.307	Hull
Os..	1.357	1.322	Hull

Li, Na, K, V, Ta, Cr, Mo, W, and alpha Fe crystallize with the body-centered lattice (see fig. 3). It is a characteristic of this lattice that each atom is symmetrically surrounded by eight other atoms. This is the closest packing for equal numbers of spheres of equal radius having opposite electric charges,

but the ordinary physical and chemical properties of these metals hardly justify a picture of half the atoms positively charged and half negatively charged. Crystals of alpha iron, and presumably of the other elements having the same structure, are quite permeable in the cold to atomic hydrogen, but not to molecular hydrogen (4). The crystal must therefore have tunnels running through it which are big enough for atomic hydrogen to pass through, but which are just too small for molecular hydrogen (effective "radius" 1.2×10^{-8} cm.) (5) to pass through at room temperature.[2]

Since the eight points of contact may be symbolized by the corners of a cube, Hull (2) assumed the shape of these atoms
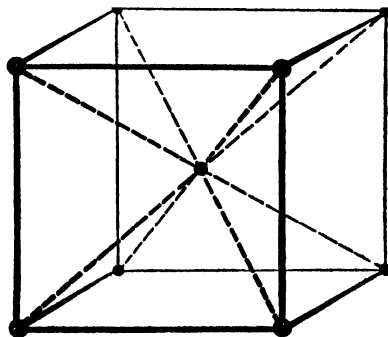
FIG. 3. BODY-CENTERED CUBIC LATTIC

to be cubic. Such an atomic shape gives tunnels of square cross section in the crystal. In alpha iron these tunnels are 1.427×10^{-8} cm. on a side. A dumb bell shaped molecule of hydrogen, 2.4×10^{-8} cm. long would be unable to fit along the diagonal of the cross section of this tunnel (2.02×10^{-8} cm.) at room temperature. Therefore no molecular hydrogen can pass very far through an iron crystal without becoming wedged in unless the temperature is such (red heat) that the tunnels become occasionally large enough by reason of the motion of the iron atoms. The diffusion of atomic carbon during the heat treatment of steel can be explained by these same tunnels

[2] The body-centered cubic structure is the closest packing for octahedra, but a closely packed structure would lack the tunnels.

(6). The diffusion of atomic carbon in Mo and W may be similarly pictured (7).

Following the precedent set by Hull, the dimensions of cubic atoms are measured in the direction of the distance of closest approach. This is along the body diagonal of the atom, and may be considered to represent the radius of the circumscribed sphere. Data are given in table 3.

TABLE 3

Equivalent radii of cubical atoms

ELEMENT	EQUIVALENT RADIUS	ELEMENT	EQUIVALENT RADIUS
(1) Li..............	1.51×10^{-8} cm.	(3) Cr.............	1.248×10^{-8} cm.
(1) Na.............	1.86	(4) Mo............	1.361
(2) K..............	2.25	(4) W.............	1.366
(1) V..............	1.32	(4) Fe............	1.236
(1) Ta.............	1.416		

(1) Hull.
(2) McKeehan.
(3) Patterson.
(4) Davey.

TABLE 4

Equivalent radii of tetrahedral atoms

ELEMENT	EQUIVALENT RADIUS
(1) C...	0.77×10^{-8} cm.
(2) Si..	1.174
(3) Ge...	1.22
(4) Sn gray...	1.40

(1) Bragg.
(2) Küstner and Remy.
(3) Hull.
(4) Bijl and Kolkmeyer.

The crystal structure of C, Si, Ge, and grey Sn are such that the atomic domains are pictured as being tetrahedra (see fig. 4) for each atom is equally distant from each of four others. This is in harmony with the mass of chemical evidence for the tetrahedral shape of C and Si. In order that the word "radius" may have any meaning in the case of tetrahedra, the dimensions of these atoms are expressed in terms of the radius of the in-

scribed sphere. This makes the "equivalent radius" equal to half the distance of closest approach. Data are given in table 4.

Frozen Hg, As, Sb and Bi, crystallize as rhombohedra, which may be regarded as being slightly distorted simple cubes. Their
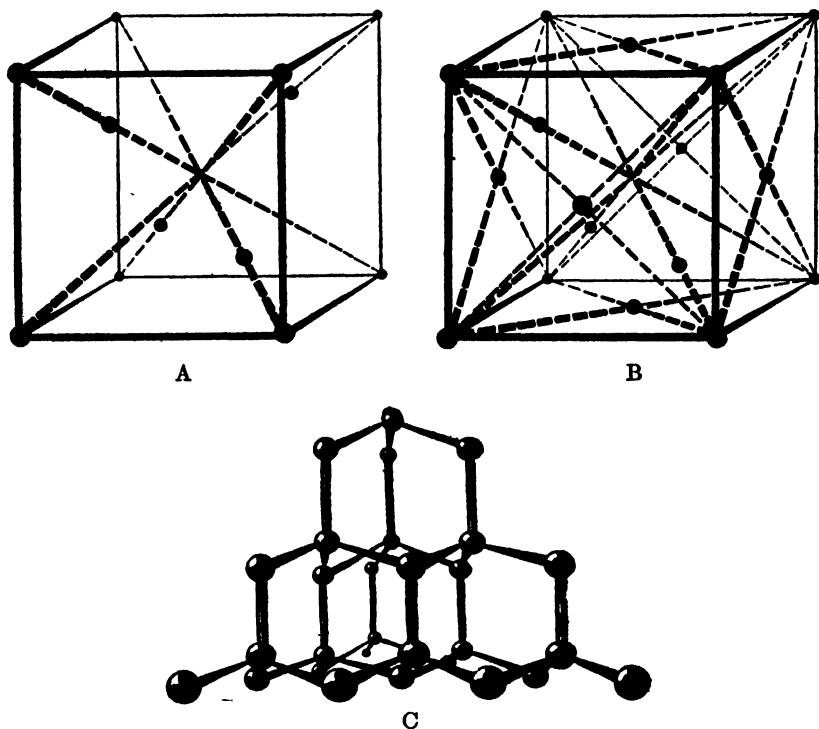
FIG. 4. DIAMOND CUBIC LATTICE

A, the superposition of figure 4A on figure 1 gives figure 4B.

B, diamond cubic lattice oriented so that one cubic axis is vertical.

C, diamond cubic lattice oriented so that the body-diagonal of the cube is vertical.

atomic domains may therefore be pictured as being distorted cubes. Their dimensions are at present unimportant.

The whole body of data on the shapes and sizes of atoms is summarized in table 5.

Although shapes and sizes were originally assigned to atoms by crystallographers in order to give a mechanistic picture of

TABLE 5

"SHAPES" AND "EQUIVALENT RADII" OF ATOMS.

GROUP O.	GROUP 1. $E_2\ O$ $E\ O$	GROUP 2. $E\ O$	GROUP 3. $E_2\ O_3$	GROUP 4. $E\ O_2$ $E\ H_4$	GROUP 5. $E_2\ O_5$ $E\ H_3$	GROUP 6. $E\ O_3$ $E\ H_2$	GROUP 7. $E_2\ O_7$ $E\ H$	GROUP 8.
H$_\epsilon$	H 1.2 L 1.51	B 1.106 1.141	B	C .77	N	O	F	F 1.236 R 1.27 N 1.237
N$_\epsilon$ A$_R$	N$_a$ 1.86 K 2.25	R 1.593 1.597 C$_a$ 1.97	A 1.430 S$_c$	A 1.174 T 1.439 1.478	P	S	C.	R 1.236 C 1.257
K$_R$	1.276 C R$_a$	1.515 1.329 B$_R$	G$_a$ Y$_r$	1.218 1.57 1.61	A$_v$ C$_b$	S$_t$ M$_o$ 1.361	B$_R$ M.	R 1.307 R 1.343 R 1.350 P 1.397
X$_\epsilon$	1.442 A C$_s$	1.714 1.480 B$_A$	I$_N$ L$_A$	1.40 A C$_a$ 1.82	A$_s$	T$_r$	I	
		RARE EARTHS			T$_a$ 2.833	W 1.366	R$_\epsilon$	O 1.355 I 1.352 P 1.385
	1.437 A	A$_u$	T$_t$	1.740 P	A$_i$			
	RADIOACTIVE ELEMENTS			1.77 T				

TABLE 6

Compressibilities of the alkali metals

ELEMENT	COMPRESSIBILITY (CALCULATED)	COMPRESSIBILITY (EXPERIMENTAL)
Li..	7.4×10^{-12}	8.8×10^{-12}
Na..	16.7	15.4
K...	38.4	31.2
Rb...	52.6	40.0
Cs...	71.4	62.5

TABLE 7

Compressibilities of polyvalent elements

ELEMENT	VALENCE	CALCULATED COMPRESSIBILITY (THOMSON)	EXPERIMENTAL COMPRESSIBILITY
Ca.................................	2	5.2×10^{-12}	5.5×10^{-12}
Al.................................	3	1.08	0.75
C..................................	4	0.178	0.16

crystal formation, these shapes and sizes have a widespread theoretical application. From them may be calculated the compressibilities of the elements, their photo-electric properties, and their relative ionizing potentials (8) (9) (10). Tables 6 and 7 compare the calculated values for the compressibility with the experimental values for the alkali metals and for Ca, Al and C. A discussion of the derivation of the equations by which the results were calculated (9) would be out of place here. It will be sufficient to state that for body-centered cubic metals (i.e., for "cubic" atoms), the compressibility is

$$\frac{1}{k} = \frac{9}{8.06} \cdot \frac{\left(\dfrac{4R}{\sqrt{3}}\right)^4}{e^2} = 31.7 \frac{R^4}{e^2}$$

where e is the charge on an electron in electrostatic units and R is the "equivalent radius" of the cubic atom. Table 8 compares the calculated and experimental photo-electric properties of alkali metals. The longest wave-length of light which will cause a photo-electric effect in an alkali metal may be calculated by the quantum relation from the work in volts required to liberate an electron from an atom. This work for cubic atoms is given by the equation (9).

$$W = -0.15 \times 4.03 \, e^2 \frac{\sqrt{3}}{4R}$$

$$= -0.262 \frac{e^2}{R}$$

Experimental data on the longest useful wave-length are available only for Li and Na. Data are, however, available for four alkali metals on the wave-length of light, which can produce the maximum photo-electric effect. It is to be expected that these wave-lengths will be proportional to the maximum wave-lengths mentioned above. That this is so is shown in table 9. Table 10 shows that the atomic radius should be roughly inversely proportional to the ionizing potential. This is in accordance with theory (8) (9).

The atomic radii of simple atoms follow a periodic law **which** is consistent with the Mendelejeff Table (11). Elements which, upon chemical combination, tend to revert to the Ni, **Pd, or Pt** type of atoms (12) are supposed to have a relatively **complex**

TABLE 8

Maximum wave length which will produce a photo electric effect

ELEMENT	CALCULATED MINIMUM VOLTAGE TO LIBERATE ELECTRON	MAXIMUM λ FOR PHOTO-ELECTRIC EFFECT CALCULATED FROM QUANTUM RELATION	MAXIMUM λ FOR PHOTO-ELECTRIC EFFECT FROM EXPERIMENT	RATIO
Li........................	2.46	5000	4500	1.11
Na........................	2.03	6100	5500	1.11

$$W = \frac{hc}{\lambda} = 0.262 \frac{e^2}{R}$$

TABLE 9

Wave length which will produce a maximum photo electric effect

ELEMENT	CALCULATED MINIMUM VOLTAGE TO LIBERATE AN ELECTRON	CALCULATED MAXIMUM λ FOR PHOTO-ELECTRIC EFFECT	EXPERIMENTAL λ FOR MAXIMUM PHOTO-ELECTRIC EFFECT	RATIO
Li..................	2.46	5000×10^{-8} cm.	2800	0.56
Na..................	2.03	6100	3400	0.56
K...................	1.63	7600	4400	0.58
Rb..................	1.53	8100	4800	0.59

$$W_1 = \frac{hc}{\lambda} = 0.262\, c\, \frac{e^2}{R}$$

TABLE 10

Relation between ionizing potential and atomic radius

ELEMENT	PACKING RADIUS OF ATOMS	IONIZING POTENTIAL	$R \times (I.P.)$
Li............................	1.51	5.37	8.1
Na...........................	1.86	5.13	9.5
K.............................	2.25	4.1	9.2
Cl............................	1.08	8.2	8.9

outer structure. They are the elements in the first five groups of Periods, 5, 7, and 9 of the periodic table. For brevity such atoms will be called "complex" atoms. The other atoms, which tend to revert upon combination to the inert-gas type of atom

will be called "simple" atoms. Excluding from consideration the first two periods of the table (i.e., H, and the period from He through F), the new law is as follows: "The ratio of the radii of any two simple atoms belonging to the same vertical column in the periodic table is the same as the ratio of the radii of any other two simple atoms on the same horizontal lines of the table provided that these atoms also belong to a common vertical column." When the atoms concerned are spheroidal, the ratio may be taken between their equatorial radii or between their axial radii. The law is illustrated in table 11. By it rough predictions may be made of the radii of the atoms of elements,

TABLE 11

Ratio of atomic radii

Ar/Ne = 1.57/1.26 = 1.25	Kr/Ar = 1.71/1.57 = 1.09
K/Na = 2.25/1.86 = 1.21	(1) Zr/Ti = 1.62/1.48 = 1.09
Ca/Mg = 1.96/1.61 = 1.22	(2 Zr/Ti = 1.59/1.45 = 1.10
(1) Ti/Si = 1.48/1.17 = 1.26	Mo/Cr = 1.36/1.25 = 1.09
(2) Ti/Si = 1.45/1.17 = 1.24	(1) Ru/Fe = 1.34/1.23 = 1.09
	(2) Ru/Fe = 1.32/1.23 = 1.07
	Rh/Co = 1.35/1.26 = 1.07

$$
\begin{aligned}
\text{Ta/V} &= 1.42/1.32 = 1.08 \\
\text{W/Cr} &= 1.36/1.25 = 1.09 \\
(1)\ \text{Os/Fe} &= 1.36/1.23 = 1.11 \\
(2)\ \text{Os/Fe} &= 1.33/1.23 = 1.08 \\
\text{Ir/Co} &= 1.35/1.26 = 1.07 \\
\text{Pt/Ni} &= 1.39/1.25 = 1.11
\end{aligned}
$$

whose crystal structure has not yet been determined. This is brought out in figure 5.

The application of atomic shapes and radii to the study of diffusion was touched on incidentally during the discussion of cubic atoms. It would make an interesting thesis for some graduate student to study the diffusion of atomic hydrogen through single crystals of all the body-centered cubic metals. Atomic dimensions are not generally useful in studying the diffusion of one metal through another, because this usually involves a consideration of the shapes and sizes of *ions* rather than of *atoms* (3). Further discussion of this point will be deferred until after the sizes of ions have been taken up.

IONIC SHAPES AND SIZES

There are, in general, two ways by which two elements may be held together in chemical combination. One is by the direct transfer of valence electrons from the atoms of one element to
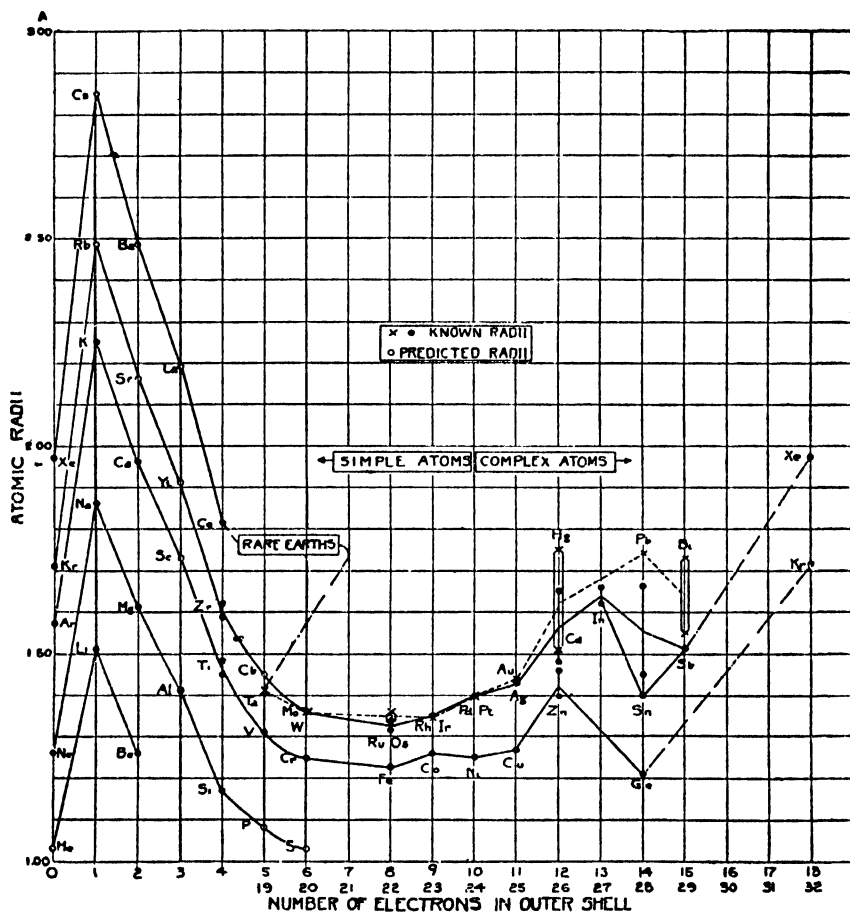

FIG. 5. PERIODIC LAW OF RADII

the atoms of the other element. The other is by the sharing of certain electrons by the atoms of both the elements. The first method produces "ionic" compounds in which the crystal of the solid is made up not of *atoms* but of *ions*. When crystals

of this sort are dissolved in water, the resulting solutions are electrically conducting. When these crystals are fused, they conduct by ionic conduction and the compound may be decomposed by electrolysis. All simple inorganic salts and all oxides and sulphides of metals with a valence of one or two are supposed to be of this sort. It is a characteristic of these compounds that they crystallize in such a way that each ion of one element is surrounded by ions of the other element, symmetrically placed and equally spaced.[3] The second method produces "non-ionic" compounds. These include the oxides of elements with a valence of three or more, many organic crystals, and such radicals as NO_3^-, CO_3^{--}, SO_4^{--}, etc.

The shape and size of an atom in the crystal of an element is, in general, quite different from that of the same element in combination, and the shape and dimensions in an ionic compound will necessarily be quite different from what they are in a non-ionic compound. If an element can have more than one valence, the ion will have a different size and shape for each valence. The radii of atoms when combined by sharing electrons are beyond the scope of this paper. Empirical estimates of these radii have been made and discussed in the well-known paper by W. L. Bragg (14). They are also discussed in the Bragg's book, "X-rays and Crystals Structure," 4th edition (Bell and Sons, 1924). There remains then to be discussed, the size and shape of the various ions.

No matter what picture we adopt of atomic structure, it is evident that the electrostatic forces inside of a "metallic" atom will be altered by the subtraction of each valence electron, with the result that the positive ion must be smaller than the neutral atom. The greater the number of valence electrons which are subtracted, the greater will be the change in the electrostatic forces and the smaller will the positive ion become. Similarly, a negative ion must be larger than the corresponding neutral atom, and the greater the valence of the element, the more

---

[3] According to Pease (13), compounds such as Si C, Cu I, Ag I, etc., which crystallize in the diamond-cubic lattice are, in a sense, non-ionic in spite of the equal spacing and symmetrical locations.

will the negative ion swell beyond the size of the neutral atom. When an attempt is made to determine the absolute sizes of these ions from crystal structure data, it is at once found that

TABLE 12

Difference between ionic radii

Differences in distances of closest approach in 10^{-8} cm.

	IODIDE	BROMIDE	CHLORIDE	FLUORIDE
Cs..........................	3.947±0 004	3.713±0.004	3.566±0.004	
Rb..........................	3.662±0.004	3.434±0.003	3.285±0.003	
Difference...............	0.285±0 008	0.279±0.007	0.281±0.007	
Cs..........................	3.947±0.004	3.713±0.004	3.556±0.004	3.084±0.003
K...........................	3.525±0 004	3.285±0.003	3.138±0.003	2.664±0.003
Difference...............	0.422±0.008	0.428±0 007	0.418±0.007	8.340±0.006
Cs..........................	3.947±0.004	3.713±0.004	3.566±0.004	3 004±0 003
Na..........................	3.231±0.01	2.968±0 003	2.814	2.310±0.002
Difference...............	0.716±0 007	0.745±0.007	0.752±0.004	0.694±9.005
Cs..........................	3.947±0.004	3.713±0.004	3.566±0.004	3 004±0.003
Li..........................	3.01 ±0.01	2 745±0.003	2 566±0.003	2 007±0 002
Difference...............	0.94 ±0 01	0.968±0.007	1.000±0.007	0.997±0 005

Differences in distances of closest approach in 10^{-8} cm.

	CAESIUM	RUBIDIUM	POTASSIUM	SODIUM	LITHIUM
I..............	3.947±0.004	3.662±0.004	3.525±0.004	3.231±0.003	3.01±.01
Br............	3.713±0.004	3.434±0.004	3.285±0.003	2.968±0.003	2.745±0.003
Difference....	0.234±0.008	0.228±0.008	0.240±0.007	0.263±0.006	0.26
I..............	3.947±0.004	3.662±0.004	3.525±0.004	3.231±0.003	3.01±.01
Cl............	3.566±0.004	3.285±0.003	3.138±0.003	2.814	2.566±0.003
Difference....	0.381±0.008	0.377±0.007	0.387±0.007	0.417±0.003	0.44
I..............	3.947±0.004		3.525±0.004	3.231±0.003	3.01±.01
F..............	3.004±0.003		2.664±0.003	2.310±0.002	2.007±0.002
Difference....	0.943±0.007		0.861±0.007	0.921±0.005	1.00

Rb salts, Havighurst, Mack and Blake.
LiI, Wyckoff and Posenjak.
All others, Davey.

the data give only n − 1 equations with which to determine n ionic radii. These n − 1 equations alone, therefore, will not enable us to calculate *radii*, but only *differences between radii*. These differences are listed in table 12 in terms of the best data available to date, using NaCl = 2.814 Å as a standard. It will be noticed that, if we exclude Li^+, Na^+ and F^-, these differences are constant for any two ions, to within the precision of the data. In other words, contrary to what might have been expected, the radii of these ions are at least approximately independent of their state of chemical combination. The fact that this is obviously untrue for Li^+, Na^+ and F^- makes it seem likely that more precise data would show slight changes in the values for the other ions. In our present state of knowledge it is sufficient to say that Cs^+, I^-, Rb^+, Br^-, K^+ and Cl^- are so much more constant in size than Li^+, Na^+ and F^- that we may consider them to act like rigid objects.

In order that we may advance from differences between radii to the radii themselves, it is necessary to make some plausible assumption which will furnish an additional equation. This assumption is furnished by the x-ray diffraction patterns themselves (15). When the diffraction patterns of the alkali halides are examined, it is found that Cs^+ and I^- have, as nearly as can be determined, equal diffracting power. Rb^+ and Br^- and K^+ and Cl^- respectively, also seem to have equal diffracting power. These three pairs are the only ones among the alkali halides for which this is so. A glance at the Periodic Table shows that each pair lies adjacent to an inert gas, and that each of the ions of each pair contains the same number of electrons as the adjacent neutral atom of the inert gas. The theory of diffraction leads us to believe that the only way in which equal numbers of electrons can show equal diffracting power is for them to be arranged similarly in atomic domains of equal volume. If our data on equality of diffracting power were quite reliable we would have three independent equations

Radius of Cs^+ = radius of I^-
Radius of Rb^+ = radius of Br^-
Radius of K^+ = radius of Cl^-

An actual trial shows that these equations are approximately true for they give fairly consistent values of ionic radii in spite of having two more equations than are needed. That they are not anything more than good approximations may be shown as follows. The periodic table would tempt us to make a fourth equation, similar to the other three, stating the equality of radii of Na^+ and F^-. But in this case the x-ray evidence clearly shows that the ten electrons in Na^+ do not have the same diffracting power as the ten in F^-, and that therefore their radii are probably different. This is not surprising when we remember that the ten in F^- are pulled inward by a nuclear charge of 9, while in Na^+ they are pulled in by a charge of 11. It would therefore seem as though the other pairs of ions were not quite of equal radius. This is confirmed by table 12, which shows that $Cs^+ - Rb^+$ is not quite equal to $I^- - Br^-$ and that $Cs^+ - K^+$ is not quite equal to $I^- - Cl^-$. Since the ions Cs^+ and I^- have the highest atomic numbers of any of the alkali and halogen ions, we will assume that the best approximation will be had by considering that their radii are equal to each other and therefore that each has a radius equal to one-half the distance of closest approach of Cs^+ and I^- in CsI. This assumption together with the differences listed in table 12 give us the ionic radii of table 13.

It will be interesting to compare these results with those of other investigators using other methods. Lande (16) assumes that since Li^+ contains only two electrons, it must l e negligibly small in the presence of I^- in LiI. This should give an upper limit for the radius for I^-. By means of table 12, lower limits are obtained for the radii of the alkali ions, and upper limits for the halogen ions. The space-lattice constants used by Lande were considerably in error, so that his results have been recalculated for table 14. Richard's values (17) depend fundamentally upon his assumption that "the contractions which occur during the formation of the alkali halides are proportional to the compressibilities of the elements concerned." His values have been recalculated using the data for CsCl which were used in table 12. Eve (18) has pointed out that the product of the ionization potential by this ionic radius is roughly a

constant. This has since been shown to have a theoretical basis (9). Saha (19) has used ionization potentials to calculate the ionic radii of metals according to this law. In comparing these radii with others, it should be remembered that they correspond

TABLE 13

Radii of the alkali and halogen ions

Cs+...............	1.974×10^{-8} cm.	I−...............	1.974×10^{-8} cm.
Rb+..............	1.696	Br−.............	1.740
K+...............	1.548	Cl−.............	1.589
Na+..............		F−...............	
in NaI...........	1.257	in CsF..........	1.030
in NaBr...... ...	1.231	in RbF....	——
in NaCl..........	1.225	in KF..........	1.116
in NaF..........	<1.15	in NaF.........	>1.15
Li+..............			
in LiI............	1.03		
in LiBr..........	1 01		
in LiCl..........	0.98		
in LiF...........	<0.86 (?)		

TABLE 14

Comparison of radii obtained by different workers

	LANDÉ	RICHARDS	EVE AND SAHA	AVERAGE	DAVEY
Cs+...........................	1.81	2 2	1.9−	2.0	1.974
I−...........................	2.14	1 7		1.9	1.974
Rb+...........................	1.51	1.9	1.7	1.7	1.696
Br−...........................	1.90	1.5		1.7	1.740
K+...........................	1.38	1.6	1.7	1.6	1.548
Cl−...........................	1.76	1.4		1.6	1.589
Na+...........................	1.09	1.5	1.4	1.3	1.1-1.2
F−...........................	1.19				1.2-1.0

to relatively high temperatures, so that they probably approximate the upper limits for the radii of positive ions. Radii obtained by these three methods have been tabulated in table 14 to the same number of significant figures as given by the original authors. The radii derived above by the present writer may

therefore be more properly compared with the average of these other radii than with any one of them alone. This comparison is made in table 14.

The crystal structure of CsI, is body-centered cubic. Since this is the closest packing for equal numbers of oppositely charged spheres of equal radius, it would appear that Cs^+ and I^- are spherical ions. This is confirmed by the fact that $CsI - CsBr$ in table 11 is, within experimental error, equal to $RbI - RbBr$ and to $KI - KBr$ in spite of the fact that the directions through the ions differ by about $54\frac{1}{2}$ degrees. The structures of the RbK and Na halides show that the shapes of $Rb^+, K^+, Na^+, Br^-, Cl^-, F^-$, are to be regarded as spheres with six flat spots, or what amounts to the same thing, cubes with rounded corners (20). These shapes are consistent with that mass of chemical data which has given rise to the "static atom" picture of atomic and ionic structure (12). The radii in such cases are measured in the direction of the distance of closest approach.

We are tempted to consider the radii of the inert gases to be half way between the radii of the adjacent ions in the Periodic Table. These radii are larger than those found by Rankine (21) from viscosity measurements. The crystal structure of solid argon has lately been determined (22). The radius of argon calculated directly from the distance of closest approach is considerably larger than that obtained in terms of K^+ and Cl^-. This is not surprising, for a crystal of argon at $40°K$ would not be under as high a state of compression as the oppositely charged ions in an ionic salt like KCl.

It has already been mentioned that the radii of ions are related to their ionizing potentials. This is not the only use for a knowledge of ionic radii. It is an experimental fact that Ag, Na and Li ions can migrate through hot glass under the influence of an electric field (23). It is found that K ions cannot travel readily through such glass, and that any attempt to force them to do so cracks the glass (24). This makes it seem as though there were tunnels of some sort through the silica framework of the glass which were large enough for Na^+ to pass through, but too

small for K⁺. A study of the diffusion of other ions through hot glasses would yield valuable information. Theoretical metallurgy offers a large field for the application of ionic radii, for it now appears that solid solutions are usually ionic rather than atomic in their nature (3). Unfortunately the use of ionic radii is limited at present because of the lack of certainty of ionic magnitudes other than of the alkalies and the halogens. Using different assumptions Pease (13) and the present writer (25) have arrived at quite different values for Cu, Zn, and Ag, and there seem to be very few other data which will serve as criteria to distinguish between the two sets of values. Data on diffusion and on the compressibilities of these ions are urgently needed.

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THE MANUFACTURE OF ALCOHOLS FROM HYDRO-
CARBONS, WITH PARTICULAR REFERENCE TO
PETROLEUM AS A RAW MATERIAL

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One of the few instances of the use of petroleum as a chemical
raw material is the conversion of the simpler unsaturated hydro-
carbons into alcohols. Curiously enough, this has been a very
recent development although the essential elements in the
chemistry of the processes now industrially employed have long
been known; oil gas has been a familiar product of various in-
dustrial processes for many years. The present industrial
development apparently arises from an effort to utilize the un-
condensed gases from cracking processes for the manufacture of
gasoline and has been greatly stimulated by the new demand
for alcohols and their acetates for the manufacture of lacquers
or varnishes in which esters of cellulose and certain varnish gums
are incorporated.[1]

One might suppose that the formation of alcohols from the
simpler olefins by the action of sulfuric acid and hydrolysis of
the resulting alkyl sulfuric esters is one of the elementary reac-
tions of organic chemistry, long known and well understood,
but in the last four years, the United States Patent Office has
granted twenty odd patents dealing with particular phases of
this reaction. This is not meant as a criticism of the Patent
Office but to emphasize that the discovery of the optimum con-
ditions under which a reaction may be carried out, any pecu-
liarities of certain raw materials or mixtures or the discovery of
conditions which materially affect the utility or practical opera-
tion of a process, constitute improvements which are patentable.
In spite of the large amount of published scientific information,

[1] D. B. Keyes, *J. Ind. & Eng. Chem.*, **17**, 558 (1925).

the subject is a very live one, industrially, and the following review will show that our knowledge of the subject is far from complete. Such substances as tertiary butyl alcohol, heretofore prepared by the well known synthesis of Butlerow by the action of acetyl chloride on zinc methyl, or by the Grignard reaction, is now available as an industrial product in large quantities.

The two raw materials of interest in this connection are petroleum and the unsaturated hydrocarbons derived therefrom by cracking, and natural gas. The relative cheapness of the gaseous olefins, as produced from petroleum in the form of oil gas, has heretofore not been taken advantage of, probably on account of the somewhat complex mixture of reactive hydrocarbons in oil gas and imperfect means of separating them usually employed.

TABLE 1

Per cent of ethylene and propylene in Pintsch gas made at different temperatures

TEMPERATURE	HIGHER OLEFINS	C_3H_6	C_2H_4	TOTAL OLEFINS
°C.	per cent	per cent	per cent	per cent
805–650	1.4	18.6	16.3	36.3
660–535	1.6	19.0	18.3	38.9
635–535	2.4	22.4	12.5	37.3
625–535	2.6	22.6	13.7	38.5
615–425	3.8	25.7	12.0	41.5

Thus, in the pioneer plant of Fritzsche, a large proportion of sulfuric acid was consumed in polymerizing or removing olefins other than ethylene without making or separating any products of value from these constituents.

Most of these products can be separated or reacted upon by chemical methods yielding reaction products of commercial value with good efficiency and also it is almost certain that by fractional distillation at low temperatures in the liquid air type of column that the major constituents of oil gas can be separated by this physical means in a state of purity satisfactory for commercial chemical synthesis. Some idea of the cost of these raw materials may be had from the fact that in commercial oil gas processes an average of 2300 cubic feet of gas per barrel (42 gallons) of oil used, can be obtained. The richest gas is pro-

duced at relatively low temperatures and as the yield of gas increases with higher temperatures, the per cent of ethylene propylene and higher olefins decreases, as is shown in the following tables. The Pintsch gas described in table 1 was purified from benzene and gasoline vapors by compressing to about 200 pounds and cooling to 15° to 20°; as the results show, it still contained some of the higher olefins, butylene and amylene.

The temperatures given are those at the beginning and end

TABLE 2

Composition of oil gas

TEMPERATURE	PRESSURE PER SQUARE INCH	ETHYLENE	PROPYLENE	HIGHER OLEFINS	TOTAL OLEFINS
°C.	pounds	per cent	per cent	per cent	per cent
600	57	19.3	28.0	3.2	50.5
650	72	19.0	28.4	4.2	51.6
700	83	17.7	23.9	3.5	45.1
730	95	17.5	20.0	3.1	40.6

TABLE 3

Per cent of oil gasified in Hall cracking unit

TEMPERATURE	OIL GASIFIED	ETHYLENE AND PROPYLENE
°C.	per cent	per cent
605	17.7	47.9
625	26.6	46.1
645	37.6	44.9
665	40.0	43.7
685	40.8 (?)	42.6
705	48.7	39.5
725	66.6	38.5

of the gas making period. The analyses were made by absorbing the higher olefins in 70 per cent sulfuric acid, the propylene in concentrated sulfuric acid, specific gravity 1.84 at room temperature and the ethylene in bromine water.[2]

The composition of oil gas made in tubes maintained at definite temperatures in an industrial size apparatus of the Hall type is shown in table 2.

[2] B. T. Brooks, *Chem. & Met. Eng.*, **22**, 630 (1920).

The relative amount of oil gasified is shown in table 3, the gas not being scrubbed or compressed for the removal of condensable light oil vapors.

As shown by M. C. Whitaker and C. M. Alexander[3] the composition of oil gas does not correspond to the equilibrium composition for the various temperatures at which it is produced, being much richer in illuminants than when the gas is subjected to these temperatures for any length of time. They suggest caution in dealing with such complex mixtures, in making deductions from one or two equilibria expressions.

The literature is very vague with respect to the composition of oil gas, the practice having been merely to condense only those tars and oils which would readily condense and only in the Pintsch gas practice has it been customary to remove light oil vapors from the gas (by compression and cooling). Consequently, the figures given for "illuminants" probably include 5 to 6 per cent of olefins other than ethylene and propylene. Nevertheless, the data for the volume of gas and its composition given by various authors is in good agreement, considering the various types of apparatus used and the many variables. The volumes of gas obtainable from various gas oils, having reference particularly to temperatures yielding gas rich in olefins, are given in table 4.

J. E. Zanetti[4] has shown that a mixture of propane and butane, separated from natural gas, gives a maximum percentage of about 38 per cent of olefins at about 750°.

If, from the above data, we take a yield of 900 cubic feet of olefins per barrel of gas oil and the proportion of ethylene, propylene and higher olefins, given first in table 1, we should have as an average yield 460 cubic feet of ethylene and 403 cubic feet of propylene. This is equivalent to 9.4 gallons of 95 per cent ethyl alcohol and 10.3 gallons of anhydrous isopropyl alcohol. This means that if the absorption of these two olefins, and their conversion to the corresponding alcohols is 80 per cent efficient, 15.7 gallons of the two alcohols are obtainable from one barrel

[3] *J. Ind. & Eng. Chem.*, **7**, 484 (1915).
[4] *J. Ind. & Eng. Chem.*, **8**, 674 (1916).

of gas oil.   In addition to these two alcohols, the butylenes and amylenes also produced yield about one gallon of secondary butyl and amyl alcohols and one-half gallon of tertiary butyl and amyl alcohols.   This takes no account of the value of the gasoline fraction which may be produced and it has been shown that such gasoline, made by the so-called vapor phase method of cracking gas oil, has peculiar merit as an anti-knock motor

TABLE 4

Yield of gas per barrel of oil

TEMPERATURE	GAS PER 42 GALLONS OIL	OLEFINS	OLEFINS	REMARKS
°C.	cubic feet	per cent	cubic feet	
743	2,990	36.6	1094	Hempel*
743	2,867	33.7	966	"
743	3,136	33.5	1050	"
785	3,320	27.3	906	"
782	3,365	27.7	932	"
682	2,490	35.8	891	Ross and Leather†
760	2,968	30.1	893	Ross and Leather
700	2,520	36.5	919	V. B. Lewes‡
800	2,870	46.2	1,325	J. F. Tocher (1)§
850	3,255	43.1	1,402	J. F. Tocher (2)
650	1,887	43.6	822	M. C. Whitaker and W. F. Rittman¶
750	2,884	30.6	882	M. C. Whitaker and W. F. Rittman

* *J. Gasbel*, **1910**, 77: various commercial gas oils used in experimental apparatus.

† *J. Gas Light'g.*, **1906**, 825: Pennsylvania Gas Oil.

‡ *J. Soc. Chem. Ind.*, **1892**, 585: Russian gas oil.

§ *J. Soc. Chem. Ind.*, **1894**, 231: Tocher used a retort 36 × 6 inches.   In (1) a gas oil of specific gravity 0.847 was used and in (2) a burning oil of specific gravity 0.807 was employed.

¶ *J. Ind. & Eng. Chem.*, **6**, 478 (1914).

fuel; a blend of ordinary gasoline containing 25 per cent of vapor phase gasoline has an anti-knock value corresponding approximately to the gasoline treated with tetraethyl lead as recommended for motor fuel use.[5]   While the proportions of

⁵ This fact does not appear to be in harmony with the theory regarding the effect of tetra ethyl lead which assumes that the lead atoms take up the ions in the gaseous explosion wave front.

the various products of cracking vary widely with the conditions of temperature and relative rate of oil passed through the cracking tubes, the above figures should indicate that this is a promising and, until recently, neglected field of industrial research.

The relative cheapness of ethylene and propylene from this source, as raw materials for the synthesis of other products, should also be pointed out. Thus, taking the catalytic conversion of ethyl alcohol to ethylene as practically quantitative, the cost of the alcohol (at 65 cents per gallon) would be $6.11 as compared with $2.73 for the gas oil, for the quantity of ethylene noted above. The difficulty, as illustrated by the attempt of Fritzsche, described below, to manufacture ethyl ether from oil gas, has been to obtain ethylene free from other olefins and to obtain values from these other products of oil cracking.

The two most important methods for the manufacture of alcohols from petroleum and natural gas are the addition of the elements of water to unsaturated hydrocarbons and the chlorination of saturated hydrocarbons (or addition of hydrogen chloride to olefins) and conversion of the chlorine derivatives to the corresponding esters or alcohols. The so-called hydration of the unsaturated hydrocarbons by means of sulfuric acid appears to be much the most important and most employed.

On account of the rather widely different properties of the different olefins and alkyl halides, the variant industrial importance of the several alcohols and the questions of considerable scientific interest in connection with these materials, the different alcohols will be discussed individually.

METHANOL

This alcohol is now being manufactured by the catalytic reduction of carbon monoxide, a subject, however, outside the plan of this review. A possible industrial synthesis is found also in the conversion of methyl chloride to methanol. The chlorination of methane has engaged the attention of a good many workers[6] and is the subject of numerous patents. No

[6] Chlorination of Natural Gas, G. W. Jones and M. H. Meighan, Bur. Mines Techn. Paper 255, (1921): Cf. also F. Martin and O. Fuchs, *Zt. Elektrochem.*, 27, 150 (1921).

industrially successful process for the manufacture of methyl chloride from methane has as yet been developed, although the conversion of methyl chloride to methanol can be accomplished with good yields by passing the chloride over hydrated lime. Methyl chloride is, of course, much more stable than the higher alkyl chlorides; E. Szarvasy[7] showed that it is slowly hydrolyzed by heating with alkali solutions at 140° (under 20 to 24 atmospheres pressure). J. R. H. Whiston[8] states that methyl chloride and steam do not react appreciably below 270° but that the formation of methanol was almost quantitative when passed over slaked lime at 300°. R. H. McKee and S. P. Burke[9] have published further details and shown that the use of steam with the lime and methyl chloride is beneficial. They estimate that with chlorine at two cents per pound, the gross cost of methanol by this method would be 70.8 cents per gallon, which figure would be somewhat reduced if the hydrochloric acid from the original chlorination could be sold. The cost of producing methanol by the catalytic reduction of carbon monoxide is probably much below this figure.

ETHYL ALCOHOL

The relationships between ethylene, ethyl hydrogen sulfate, ethyl ether and ethyl alcohol, were pointed out by H. Hennell,[10] as long ago as 1828, who stated "thus ether may be formed from alcohol, and alcohol from ether at pleasure by throwing the hydrocarbon of these bodies into that peculiar state which it assumes when combined with sulfuric acid. We may even proceed beyond this, and form either alcohol or ether, using olefiant gas as the hydrocarbon base; for as I have shown . . . . olefiant gas, by combining with sulfuric acid, forms sulfovinic acid, and the acid so produced forms either ether or alcohol, according to circumstances which are under perfect control."

[7] *J. Soc. Chem. Ind.*, **35**, 707 (1916): B. S. Lacy, U. S. Pat. 1, 253, 615 (1918), heats methyl chloride with milk of lime in an autoclave to temperatures above 100°.

[8] *J. Chem. Soc.*, **117**, 190 (1920).

[9] *J. Ind. & Eng. Chem.*, **15**, 682, 788 (1923).

[10] *Phil. Trans. Royal Soc.*, **1828**, 365.

M. Berthelot[11] absorbed ethylene in concentrated sulfuric acid, diluted the acid mixture with 5 to 6 volumes of water and distilled, thus obtaining a very good yield of ethyl alcohol. He also showed that by adding sodium acetate, potassium butyrate or benzoate directly to the acid solution and distilling, the corresponding ethyl ester could be obtained.[12]

The manufacture of ethyl alcohol from the ethylene in coal gas was suggested at an early date and alcohol made in this way was exhibited at the London Exhibition in 1862. An industrial attempt was made about that time in St. Quentin, France, but was soon abandoned.[13]

In an early English patent, E. A. Cotelle stated that the gas should first be purified from oil vapors and hydrogen sulfide and also that the propylene, amylene and similar hydrocarbons should be removed by scrubbing with sulfuric acid.[14] He also suggested the use of oil gas for this purpose and describes diluting the resulting acid mixture with water and distilling to obtain the alcohol.

An industrial plant for the conversion of ethylene into ethyl ether was operated by P. Fritzsche in Richmond, Va., in 1900 and 1901. Oil gas was the source of the ethylene. In his English Patent 20,225 (1896) Fritzsche claims the preliminary treatment of oil gas, coal gas and similar gases containing ethylene and other olefins, with cold concentrated sulfuric acid to absorb olefins other than ethylene, and following this by scrubbing with concentrated sulfuric acid at 100 to 140°. In another patent[15] he describes treating the gas first with acid containing 80 per cent H_2SO_4 at 70° to 80° to remove propylene

[11] *Ann. de Chim. et de Phys.* (3), **43**, 385 (1855).

[12] C. Ellis and M. J. Cohen, U. S. Pat. 1,365,050 (1921), have patented the process adding sodium acetate to the sulfuric acid solution, containing alkyl sulfuric esters, obtained from oil gas, and distilling to get ethyl, propyl and butyl acetates: in U. S. Pat. 1,365,051 the mixture of acetates is claimed as a new composition of matter and in U. S. Pat. 1,365,049, the use of this mixture of esters as a solvent is patented.

[13] Payen, *Dinglers Polytechn. J.*, 167, 236 (1863).

[14] English Pat., 2062 (1862): Eng. Pat. 1924 (1863).

[15] German Pat. 89,598 (1897).

and butylene. The ethylene was passed through four scrubbing towers in which sulfuric acid at 100° to 120° was passed, countercurrent to the ethylene. He pointed[16] out that temperature control is necessary and that provision must be made to hold the temperature of the first scrubbing towers below 40°, and that if the acid from these preliminary scrubbers is diluted with three to four parts of water and distilled isopropyl alcohol is produced; oily polymers were also formed.

Apparently undeterred by the failure of Fritzsche's plant, which made use of oil gas containing a large percentage of ethylene, others have more recently taken up the problem and endeavored to use coal gas containing up to about 2.5 per cent of ethylene. The gas must first be well purified from hydrogen sulfide and other sulfur compounds as well as aromatic hydrocarbon vapors and all ethylene homologues.[17] E. Bury has described the work done at the plant of the Skinninggrove Iron Co.,[18] and reports that at 60° to 80° about 71 per cent of the ethylene in the gas was absorbed and that 70 per cent of the absorbed gases were recoverable as ethyl alcohol, the amount of the latter being equivalent to about 1.6 gallons of alcohol per ton of coal.

The earlier observations, with regard to the conditions for the reaction of ethylene and sulfuric acid were only qualitative, but S. G. P. Plant and N. V. Sidgwick[19] have studied the reaction of ethylene and propylene with sulfuric acid and found that at 70° the reaction with ethylene could be carried out practically to completion with 98.8 per cent of 100 per cent acid without any sign of decomposition; considerable decomposition was noted after 2.5 hours at 100°. Their results for the absorption of ethylene at 50° and 70° are given in tables 5 and 6. The formation of diethyl sulfate in substantial proportions is of

[16] *Chemische Ind.*, **35**, 638 (1912).

[17] F. S. Sinnatt, (*Gas Journal*, **1920**, 695) prepared the dibromides of the olefins in a typical coal gas and on the basis of the fractional distillation of this mixture gives the following *relative* percentages, ethylene 84.3 per cent, propylene 11.8 per cent, butylene 2.3 per cent, amylene, etc., 1.5 per cent.

[18] *Gas Journal* (**1919**) 718.

[19] *J. Soc. Chem. Ind.*, **40**, 15T (1921).

particular interest and since it is readily separated as a heavy oil merely by diluting the acid reaction mixture, this should prove to be an excellent method for the manufacture of this valuable ethylating reagent.

C. F. Tidman[20] also states that in large scale work the best temperature for ethylene absorption by 95.4 per cent acid is 60° to 80°.

TABLE 5

Absorption of ethylene at 50°

TIME	CONCENTRATION OF H_2SO_4		
	93.1 per cent	97.6 per cent	99.3 per cent
hours			
3	1.24	1.70	2.52
9	3.63	5.49	9.38
15	6.39	10.90	21.63
26	12.51	24.49	32.01*

* This analyzed 72.7 per cent ethyl hydrogen sulfate and 22.2 per cent diethyl sulfate.

TABLE 6

Absorption of ethylene at 70°

CONCENTRATION OF H_2SO_4

----	93.1 per cent	95.8 per cent	98.8 per cent
hours			
2.5	1.36	1.28	2.75
10	6.59	8.05	17.16
15	10.59	13.95	28.50
20	18.19	24.48	34.39

C. Maimeri[21] has recently published data which show the benefit of absorbing the ethylene in acid under pressure. His investigation was evidently carried out with pure ethylene but he states that 1300 cubic meters of coke oven gas containing 4 per cent ethylene (much higher ethylene content than gas made by American practice) will yield 64 kgm. of ethylene by absorption in ethyl alcohol, 100 kgm., under pressure. After

[20] *J. Soc. Chem. Ind.*, **40**, 86T (1921).

[21] *Chem. Abst.*, **19**, 1402 (1925).

absorbing the ethylene in sulfuric acid, 98 to 100 per cent the mixture was diluted with water and ice to separate diethyl sulfate. Working at 3.5 atmospheres pressure the yield of diethyl sulfate was 35 per cent and ethyl hydrogen sulfate 51 per cent based on the acid used; at 10 atmospheres the yield of diethyl sulfate was 62 per cent and ethyl hydrogen sulfate 30 per cent; the total yield of ethyl alcohol, at 10 atmospheres absorption pressure, was 76.7 per cent. The temperatures employed are not given. Maimeri alludes to the high acid consumption of earlier work but it should be noted that, as in the operation of Fritzsche's plant, the excessive acid consumption is caused largely by the acid required for preliminary purification of industrial gases such as oil gas or coke oven gas. Present developments in this country utilize oil gas from various sources for the ethylene homologues and only one manufacturer is making use of ethylene and in this case it is converted into ethylene chlorohydrin and glycol.

A. Damiens[22] states that small proportions of water greatly retard the reaction, 99.5 per cent acid absorbing ethylene at three to five times the rate shown by 95 per cent acid; the rate of absorption at 60° is three times the rate at 25°. He also confirms the fact that decomposition of the acid solution is appreciable above 60°. As noted above, the formation of diethyl sulfate is considerable when 100 per cent acid is employed, and at 15° an equilibrium mixture is reached containing 35.6 parts of diethyl sulfate per 100. Increase in temperature or dilution shifts the equilibrium in favor of ethyl hydrogen sulfate. The rate of absorption of the gas is also directly proportional to the pressure and the surface of contact. A semi-commercial plant, using oil gas, is described by Damiens and E. de Loisy,[23] the gas being given a preliminary washing with sulfuric acid as in Fritzsche's process.

A number of patented processes deal with the purification[24] of

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[22] *Bull. Soc. Chim. de France*, (4), **33**, 71 (1923): *Compt. rend.*, **175, 585** (1922).
[23] *Chimie et Industrie*, **1923, 664.**
[24] C. Still, Eng. Pat. 147,737 (1920), specifies a sequence of operations, finally treating the gas with sulfuric acid 50° Be and later with acid of 66° Be.

the gas and with the concentration or isolation of ethylene. F. Soddy[25] separates ethylene from hydrogen, methane and carbon monoxide by absorption of the ethylene in activated charcoal. E. Berl and O. Schmidt[26] show the enrichment of ethylene by successively treating a gas containing 17.08 per cent ethylene with activated charcoal, of 64.2 per cent, 90.9 per cent and by the third treatment 98.8 per cent ethylene. They note that vapors of heavier hydrocarbons displace the ethylene from the charcoal.

G. O. Curme[27] prepares a gas rich in ethylene by compressing, cooling and absorbing the ethylene in acetone, releasing the ethylene by releasing the pressure. I. Brown[28] purifies the gas and separates nearly pure ethylene by liquefaction and fractional distillation at low temperatures.

The rate of the reaction of ethylene and sulfuric acid is affected catalytically by certain substances. A Damiens[29] states that cuprous salts are most effective, iron salts less so and R. Engehardt and W. Lommel[30] state that silver sufate has a very pronounced effect on the rate of absorption. With silver, mercurous and cuprous salts, the reaction proceeds in two stages, ethylene first forming a compound with the metal salt and later reacting with the acid. With silver sulfate this absorption takes place readily even in very dilute acid solution; thus a silver sulfate solution containing 3 per cent sulfuric acid readily absorbed one mol. of ethylene. W. Glund and G. Schneider[31] state that the reaction of ethylene and sulfuric acid is accelerated by the sulfates of calcium, lead, iron, copper, ferrous ammonium sulfate and silver, the last being most effective. The compounds of ethylene with mercury salts have long been known. J. Sand and F. Breest[32] noted that the formation of mercuric ethanol chloride

[25] U. S. Pat. 1,422,007 and 1,422,008.
[26] Z. f. Angew. Chem., 36, 247 (1923).
[27] U. S. Pat., 1,422,184.
[28] German Pat. 338,358 (1916).
[29] Compt. rend., 175, 585, (1922): Brit. Pat. 180,988 (1922).
[30] Ber. 57 B, 848 (1924): U. S. Pat. 1,458,646.
[31] Ber. 57 B, 254 (1924).
[32] Z. f. physik. Chem., 59, 424 (1907): 60, 237 (1907).

was reversible and W. Schoeller[33] showed that mercuric acetate in methanol solution readily absorbed 1 mol. of ethylene, the gas being expelled by warming with hydrochloric acid. One process of separating ethylene from inert gases is based upon the use of mercuric sulfate.[34] W. Manchot and W. Brandt[35] have called attention to the fact that the absorption of ethylene by copper salts causes serious errors in gas analyses unless entirely removed before determining carbon monoxide.

Ethylene and water react only very slightly, in the absence of catalysts, at elevated temperatures and pressures. H. W. Klever and F. Glaser[36] found that in 17 hours at 150° and 190 atmospheric pressure only 0.00011 mol. of ethylene was hydrated; at 200° and 100 atmospheric pressure 0.0008 mol. was hydrated, but by adding 1.93 per cent of hydrochloric acid more than one mol. was hydrated from which they concluded that ethyl chloride was first formed and this then hydrolyzed.

When pure ethylene and steam are passed together over alumina or aluminum sulfate at 360°, very small proportions of acetaldehyde are formed, from which J. P. Wibaut and J. J. Diekmann[37] conclude that ethyl alcohol is first formed. They also note that at 156° to 160°, 55 per cent sulfuric acid does not react with ethylene and 65 per cent acid only very slowly.

Ethylene reacts readily with chlorosulfonic acid and 86 per cent of the reaction product is hydrolyzed by water to form ethyl alcohol and 16 per cent to form ethyl chloride. W. Traube and R. Justh[38] recommend the use of equal parts of 100 per cent sulfuric acid and chlorosulfonic acid.

Ethylene and hydrogen chloride react to give ethyl chloride; E. Berl and J. Bitter[39] report a yield of 36 per cent using anhydrous aluminum chloride and HCl at 130° to 170°. G. Curme[40]

[33] *Ber.* **46**, 2864 (1913).
[34] U. S. Pat. 1,315,541 (1919).
[35] *Ann.*, **370**, 286 (1909): **420**, 170 (1920).
[36] *Chem. Abs.*, **18**, 1976 (1924).
[37] *Chem. Abs.*, **17**, 3858 (1923).
[38] *Brennstoff-Chem.*, **4**, 150 (1923).
[39] *Ber.* **57 B**, 95 (1924).
[40] U. S. Pat. 1,518,182 (1924).

states that satisfactory commercial yields of ethyl chloride can be obtained by treating ethylene with hydrogen chloride under a pressure of about 160 atmospheres without a catalyst and also at about 35 atmospheres in the presence of aluminum chloride; no temperatures are given.

Very little has been published regarding the conditions advantageous for the conversion of ethyl chloride to ethyl alcohol or other products. B. S. Lacy[41] passes the chloride over calcium oxide at 250° to 450°. Williamson's well known synthesis of ethyl ether was carried out with ethyl iodide. In J. U. Nef's researches on ether formation from alkyl halides, ethyl bromide and iodide were employed, but not the chloride, although with other alkyl halides he showed that in a series of so-called double decomposition reactions the formation of the olefins was maximum with the alkyl iodides and minimum with the alkyl chlorides.[42] The reactions of ethyl chloride and its preparation from industrial gases offers an attractive field for investigation with industrial possibilities.

ISOPROPYL ALCOHOL[43]

Berthelot[44] showed that alcohols could be made from ethylene homologues by combining the olefins with sulfuric acid and hydrolyzing the resulting sulfuric acid ester; he made isopropyl alcohol in this way and believed that the reaction was a general one. He showed that one volume of concentrated sulfuric acid absorbed about 860 volumes of propylene at 18°, and on subsequent treatment with water both isopropyl alcohol and oily

[41] U. S. Pat. 1,245,742 (1917), Lacy chlorinates ethane at temperatures above 300° and states that it chlorinates much more readily than methane; U. S. Pat. No. 1,242,208.

[42] Ann., **309**, 126 (1899).

[43] In 1920 C. Ellis gave an account of the manufacture of isopropyl alcohol from cracking still gases (Chem. & Met. Eng., **23**, 1230 (1920)). A small experimental plant was built near the Bayonne plant of the Tidewater Oil Co. and later the Standard Oil Co. of New Jersey secured the rights to the process and is now producing isopropyl alcohol, under the name of petrohol, at its Bayway refinery.

[44] Ann., **127**, 69 (1863): Ann de chimie et de phys., (5) **9**, 289 (1876); (7) **4**, 104 (1895).

hydrocarbon polymers were obtained. Fritzsche and others who converted the ethylene of oil gas, coal gas and the like into ethyl alcohol employed sulfuric acid to remove the propylene and other olefins; Fritzsche[45] removed propylene by treating with cold concentrated sulfuric or by sulfuric acid of not over 80 per cent at 70° to 80°.[46] He examined the products of hydrolysis of the acid used for removing the propylene and found isopropyl alcohol but he apparently made no attempt to conserve this product or to determine the best operating conditions to obtain this alcohol. Plant and Sidgwick[47] state that propylene is readily absorbed by 97 per cent sulfuric acid at 25° and that 80 per cent and 90 per cent acid also absorbs propylene at roughly the rate that ethylene is absorbed by 100 per cent acid at 70° but beyond noting the formation of hydrocarbon polymers say nothing as to the yield of isopropyl alcohol obtained by hydrolysis. J. U. Nef[48] was obviously in error when he stated that ethylene, propylene and butylene could be estimated by treating the gas mixture with concentrated sulfuric acid at 0°; he stated that the ethylene passed through unchanged; the propylene formed isopropyl sulfuric acid which could be determined by hydrolyzing to the alcohol and distilling and that the butylenes were polymerized to heavy hydrocarbon oil. Both propylene and butylene yield hydrocarbon polymers and some of the corresponding alcohols under these conditions.

The patents having to do with the industrial manufacture of isopropyl alcohol from the propylene in oil gas, the uncondensed gas resulting from cracking heavy oil for gasoline and usually known as cracking still gas, deal with particular features not fully disclosed by the older literature. They are chiefly of interest as illustrating the improvements or new details of operation which are patentable.

M. D. Mann and R. R. Williams[49] describe passing gas con-

[45] English Pat. 20,225 (1896): *J. Soc. Chem. Ind.*, **16**, 824 (1897).

[46] *J. Soc. Chem. Ind.* 16,630 (1897): *Chem. Industrie*, **35**, 637 (1912).

[47] *Loc. cit.*

[48] *Ann.*, 318, 26 (0000).

[49] U. S. Pat. 1,365,043 (1921).

taining propylene through an agitated mixture of sulfuric acid of about 1.8 specific gravity and neutral oil at temperatures below 30°. C. Ellis[50] claims as a solvent the mixture of the acetates derived from the simpler iolefins or their alcohols, such as ethyl, isopropyl and secondary butyl alcohols.

C. Ellis and M. J. Cohen[51] claim the treatment of the sulfuric acid solution resulting from the treatment of oil gas and the like with sodium acetate to obtain a mixture containing ethyl, isopropyl and secondary butyl acetates. H. E. Buc[52] has patented the chlorination of isopropyl alcohol at 35° to 75°, and continuing the chlorination above 70° to obtain pentachloroacetone. In another patent[53] Buc describes raising the temperature as the chlorination proceeds. When isopropyl alcohol is partially chlorinated a mixture consisting principally of di- and tri-chloroacetones results.[54] Buc[55] has also patented the conversion of isopropyl alcohol to isopropyl chloride by treating with dry or aqueous hydrochloric acid and distilling the mixture. C. Ellis and A. A. Wells[56] pass chlorine into a solution of olefins in sulfuric acid but the products are not very definitely characterized. M. C. Mann[57] has patented the dehydration of isopropyl and other alcohols, the process consisting in adding caustic soda and separating the two layers thus formed. Buc has also patented the dehydration of alcohols by mixing with kerosene and heating with lime.

R. R. Williams and D. H. White[58] have patented the oxidation of isopropyl and other secondary alcohols to ketones by passing the vapors with air over brass at 500° to 800°. The polymerization of propylene and other olefins to hydrocarbon oils has been referred to above; the polymerization of the olefins in oil gas

[50] U. S. Pat. 1,365,049 (1921).
[51] U. S. Pat. 1,365,050 (1921).
[52] U. S. Pat. 1,391,757 (1921).
[53] U. S. Pat. 1,391,758 (1921).
[54] U. S. Pat. 1,436,378 (1922).
[55] U. S. Pat. 1,436,377 (1922).
[56] U. S. Pat. 1,440,976 (1923).
[57] U. S. Pat. 1,452,206 (1923): 1,455,072 (1923).
[58] U. S. Pat. 1,460,876 (1923): also A. A. Wells, U. S. Pat. 1,497,817 (1924).

by means of sulfuric acid (conditions not definitely specified) has been patented by C. Ellis.[59]   The use of alcohols or ketones, derived from petroleum olefins, mixed with gasoline as a motor fuel has also been claimed by C. Ellis.[60]   Another patent issued to Ellis[61] specifies the preliminary purification of the gas, treating with sulfuric acid specific gravity 1.8 together with several volumes of inert oil to remove propylene and then treating the gas with an acid stronger than 1.8 at above 60°.   The conversion of isopropyl alcohol to isopropyl ether by boiling with sulfuric acid, 70 to 85 per cent, is claimed by M. D. Mann:[62] the yield is stated to be about 40 per cent of the theory.   When the usual process of esterification is carried out with isopropyl alcohol and acetic acid W. W. Clough and C. O. Johns[63] find that a constant boiling mixture is formed containing about 47.5 per cent isopropyl acetate and 52.5 per cent isopropyl alcohol.   Various special processes of refining isopropyl alcohol have also been patented, for example treating with potassium permanganate,[64] alkaline hypochlorite solution,[65] dissolving in sulfuric acid of about 1.57 specific gravity and diluting, distilling or extracting the alcohol,[66] filtering through sawdust.[67]

According to W. W. Clough and C. O. Johns[68] the industrial manufacture of isopropyl and other secondary alcohols, from oil gas or petroleum cracking still gas was due largely to the efforts of M. D. Mann, Jr.   An important step in this work was the discovery by M. D. Mann and R. R. Williams that a mixture of inert hydrocarbon oil and sulfuric acid absorbed propylene from gases lean in this constituent much more readily than when sulfuric acid alone was used.   Clough and Johns

[59] U. S. Pat. 1,464,152 (1923).
[60] U. S. Pat. 1,412,233 (1922).
[61] U. S. Pat. 1,464,153 (1923).
[62] U. S. Pat. 1,482,804 (1924).
[63] U. S. Pat. 1,485,071 (1924).
[64] M. D. Mann, U. S. Pat. 1,518,339 (1924): 1,491,916 (1924) and U. S. Pat. 1,502,149 (1924).
[65] H. E. Buc, U. S. Pat. 1,498,229 (1924).
[66] C. Ellis and M. J. Cohen, U. S. Pat. 1,365,048 (1921).
[67] M. D. Mann, U. S. Pat. 1,413,864 (1922).
[68] *Ind. & Eng. Chem.*, **15**, 1030 (1923).

note an azeotropic mixture containing 91 per cent of alcohol and 9 per cent of water (by volume) boiling at 80.4° and having a specific gravity at 20°/4° of 0.816. The anhydrous alcohol boils at 82.4°. Isopropyl alcohol and the acetate also form an azeotropic mixture containing 52.3 per cent of the alcohol and 47.7 per cent of the ester (by weight).

<div align="center">INDUSTRIAL OPERATION</div>

Isopropyl alcohol is at present the most important, industrially, of the several alcohols now being manufactured from oil gas, or cracking still gases. Three manufacturers have a combined production of about 575,000 gallons of isopropyl alcohol annually. The oil gas, or cracking still gas is first treated to remove all condensible hydrocarbons valuable as gasoline. This practice is now quite general in the larger refineries, whether the residual gases are chemically utilized or not. Usually all of the waste gases, including uncondensed vapors from the stills, are brought together and treated by well known methods for removal of gasoline vapor, and where the residual gas is to be chemically treated, this should include scrubbing the gas with heavy oil under pressure. The scrubbed gas is then given a preliminary treatment with dilute sulfuric acid to remove butylenes and amylenes, the concentration and temperature of the acid varying with different manufacturers, the object being to convert as large a percentage as possible of the butylenes and amylenes into alcohols. As noted above, Fritzsche merely polymerized these olefins, which accounts largely for the very high acid consumption in his process. In accordance with well known practice in handling sulfuric acid, the scrubbing towers using dilute sulfuric acid are lead lined, but where the concentration is 80 per cent or more, cast iron or steel is used. The gas is passed counter-current against the acid in the scrubbing towers, several such towers being arranged in series. The acid from the last tower containing isopropyl hydrogen sulfate together with polymers and small proportions of di-isopropyl sulfate is diluted with water, separated from the oily mixture of polymers and distilled with steam to obtain
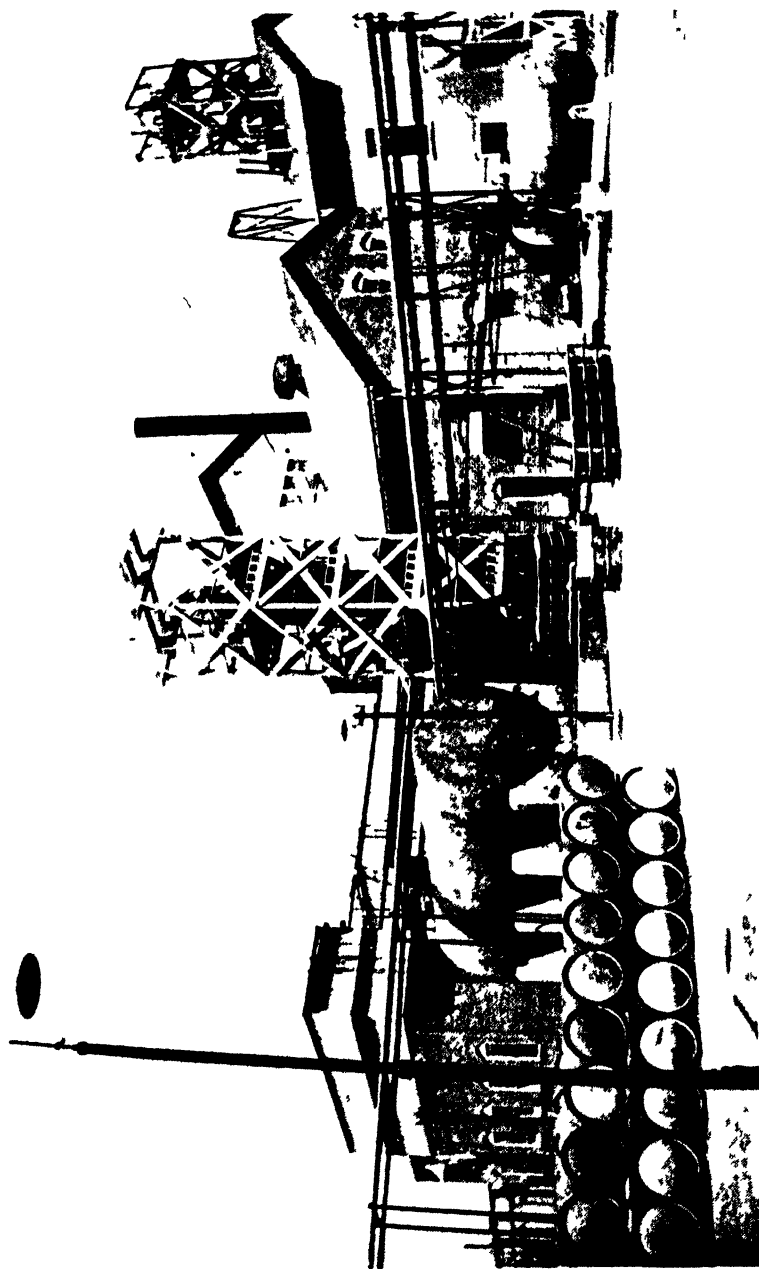
Plant of Empire Refining Co for Manufacturing Alcohols from Cracking Still Gases

dilute isopropyl alcohol. A small proportion of hydrocarbon polymers are separated from the dilute isopropyl alcohol distillate and the dilute alcohol then concentrated by fractional distillation. The crude isopropyl alcohol contains traces of malodorous substances, probably mercaptans, which are removed by hypochlorite or other oxidizing reagents. Well refined isopropyl alcohol has an odor closely resembling ethyl alcohol, and the solvent power and physical properties of the anhydrous isopropyl alcohol make it an excellent substitute for ethyl alcohol for certain uses, and with the further advantage of not being subject to the manifold government regulations, applied to ethyl alcohol.

Secondary butyl, amyl and hexyl alcohols are recovered by diluting the acid employed for removal of the corresponding olefins, prior to the absorption of the propylene. The diluted acid solution is distilled with steam and the dilute mixture of alcohols thus obtained are concentrated and separated by fractional distillation. Final dehydration may be carried out by adding solid caustic soda, which causes separation into two layers, and distilling the alcohol layer, or by adding a low boiling liquid such as benzol and distilling, the benzene carrying over the water present.

Butyl alcohols

The ease with which isobutylene reacts with dilute sulfuric acid was recognized by Butlerow[69] who dissolved isobutene in a mixture of equal parts of sulfuric acid and water; at ordinary temperatures the hydrocarbon slowly dissolved without appreciable discoloration or separation of hydrocarbon polymers. After neutralizing the acid solution and distilling, a nearly theoretical yield of *tertiary butyl alcohol* was obtained. If the acid solution is warmed the hydrocarbon polymers quickly form. He also noted that normal butene-2 was noticeably less reactive to sulfuric acid than isobutylene, but could similarly be converted to normal secondary butyl alcohol. In this case, an acid mixture of two parts of acid to one of water required several

[69] *Ann.*, **180**, 245 (1875).

days at ordinary temperature to effect solution, whereas iso-butene was completely converted in a few hours, under the same conditions. He later[70] stated that this acid mixture and also one consisting of three parts of acid to one of water gave "small quantities" of hydrocarbon oil at ordinary temperatures: con-centrated sulfuric acid promptly gave a mixture of hydrocarbon polymers of high boiling point. The polymer formed by warming with equal parts of acid and water, to 100°, is chiefly di-isobutylene.

A. Michael and R. F. Brunel[71] found that isobutene is the most reactive olefin known, to sulfuric acid and halogen acid. The greater reactivity of isobutene as compared with normal butene was found to be as follows, the hydrocarbons in gaseous form being passed through the acid.

	PARTS H_2SO_4 TO 1 PART H_2O (BY WEIGHT)	TEMPERATURE OF ACID	PER CENT ABSORBED
Isobutene.............................	2	17°	100
Butene (2).............................	2	15°	12
Butene.................................	3.5	18°	None
Butene.................................	3.75	18°	37
n. butene (1)...........................	3.75	17°	33
n. butene.............................	4	17°	49

With dilute sulfuric acid, 50 per cent by weight, isobutene dissolved completely in twenty minutes, trimethyl ethylene in two hours. Tetramethyl ethylene is still much less reactive: in 66 per cent acid trimethyl ethylene readily dissolves but tetramethyl ethylene was not appreciably dissolved after six hours. Since oil gas contains isobutene, butene -2 and probably butene -1, and probably all the isomeric amylenes with the possible exception of isopropyl ethylene and normal pentene -1 it is apparent that the concentration of the acid employed is of the greatest importance.

W. W. Clough and C. O. Johns[72] have described secondary

[70] *Ann.*, **189**, 46 (1877).
[71] *Am. Chem. J.*, **41**, 118 (1909).
[72] *J. Ind. & Eng. Chem.*, **15**, 1030 (1923).

butyl alcohol made by treating pressure still gases with sulfuric acid and hydrolyzing the butyl sulfuric ester and have noted that this alcohol forms an azeotropic mixture with water which boils at 87.5° and contained 72.7 per cent of the alcohol by weight, or 77.72 per cent by volume. They give the physical constants of this alcohol as follows: boiling point of the anhydrous alcohol, 99.40° at 760^{mm}, D at 15°/4° 0.8104, 20°/4° 0.8063. These authors have also determined the specific gravity of aqueous solutions of the alcohol; the saturated aqueous solution at 20° contains 17.85 per cent by weight or 21.55 per cent by volume of the alcohol and has a density of 0.9732 20°/4°: the alcohol phase at 20° contains 64.17 per cent by weight or 69.97 per cent by volume of the alcohol and has a density of 0.8792, 20°/4°. They also note that secondary butyl alcohol and its acetate form an azeotropic mixture boiling at 99.60° (758^{mm}) and consists of 86.3 per cent alcohol and 13.7 per cent of the ester, by weight.

R. R. Read and F. Prisley[73] converted isobutene to the tertiary alcohol by treating it in solution in kerosene with cold 50 per cent sulfuric acid. As noted by others[74] a rearrangement of butylenes occurs on heating and on dehydrating isobutyl alcohol over alumina at 450° to 475° these authors obtained 30 to 35 per cent of butene -2, which was not absorbed by the 50 per cent acid at 0° to room temperature. From 1000 g. of isobutyl alcohol they obtained 550 g. tertiary butyl alcohol melting above 15°. The acid solution containing the alkyl sulfuric ester was run into an excessive of alkali, vigorously stirred.

In connection with the conversion of the butenes and amylenes to alcohols by means of sulfuric acid, it is of interest to note that none of the many workers who have prepared secondary and tertiary alcohols in this way have observed the formation of any primary *alcohols*. According to A. Michael and Leighton,[75] who were interested in a study of Markownikows rule,

[73] *J. Am. Chem. Soc.*, **46**, 1512 (1924).

[74] Nef. *Ann.*, **318**, 22 (1901): Senderens, *Compt. Rend.*, **144**, 1110 (1907); Ipatiev, *Ber.* **36**, 2012 (1903).

[75] *J. Prakt. Chem.*, **60**, 286, 443 (1899).

propylene and hydriodic acid yields a very small proportion of normal propyl iodide, and isobutene and hydrogen bromide in acetic acid yields about 93 per cent tertiary butyl bromide and 7 per cent of the primary isobutyl bromide.

Amyl alcohols

Commercial amylene as used by earlier workers was a mixture of amylenes prepared by the decomposition of fermentation amyl alcohol.   Berthelot[76] stated that ordinary sulfuric acid almost completely polymerizes this hydrocarbon mixture. Erlenmeyer[77] tried sulfuric acid of various concentrations but on diluting and distilling (without neutralization) obtained no amyl alcohols.   A little later Flavitsky[78] stated that he obtained a mixture of amyl alcohols boiling from 100° to 108° by treating a commercial amylene mixture with dilute sulfuric acid, containing 2 parts of concentrated acid to one part of water.   He diluted the acid mixture but did not neutralize it before distilling. The yield is not stated but he notes the formation of the polymer boiling at 155° to 160°.   A Wischnegradsky[79] worked more carefully and treated commercial amylene (made from fermentation amyl alcohol) with a mixture of equal parts by volume of concentrated sulfuric acid and water, keeping the mixture cold by snow and salt.   About half of the amylene was dissolved, the resulting mixture passed into a mush of snow and neutralized by caustic soda.   The alcohol obtained was chiefly the tertiary alcohol, the so-called amylene hydrate or dimethyl ethyl carbinol.   Wischnegradsky also noted that normal pentene -2 and isopropyl ethylene were much less reactive to sulfuric acid than trimethyl ethylene.   He converted fermentation amyl alcohol to the iodides and from this made the amylenes by caustic potash.   On treating the amylene mixture with acid containing two volumes of acid to one of water, at 0°, about 38 per cent went into solution.   The residual oil contained some

[76] *Ann.*, **127**, 69 (1863).
[77] *Zt. fur. Chemie & Pharm.*, **1865**, 362.
[78] *Ann.*, **165**, 157 (1873).
[79] *Ann.*, **190**, 328 (1878).

polymer but isopropyl ethylene boiling sharply at 21.5° was easily separated from it.

No accurate work on the nature of the amylenes produced by cracking petroleum oils at different temperatures, the relative amounts of each present or the relative stability of the different amylenes to heat, has been published. The nature of the oils which separate when sulfuric acid, which has been used for refining gasoline or kerosene, is diluted with water long remained a mystery, although the odor of secondary alcohols in such "acid oils" is usually very pronounced. R. Zaloziecki[80] stated "by the dilution of the sludge acid with water, the constituents soluble in concentrated acid separate out again, while other reactions take place which give rise to alcohols, ketones and ethers, but principally to polymers."

J. Hausman[81] showed the presence of so-called sulfo acids in the diluted mixture which form water-soluble barium salts. It is now known that on treating mixtures of unsaturated hydrocarbons, such as the commercial cracked gasolines, with sulfuric acid 85 to 93 per cent, cooled or at ordinary temperatures, alcohol formation results chiefly in the case of the simpler olefins and that while some polymers and alkyl sulfuric esters are formed, polymerization is the chief result with olefins of more than six carbon atoms.[82]

In the treatment of amylenes or hexylenes with sulfuric acid 85 to 93 per cent and subsequently diluting the acid solution with cracked ice and water a certain amount of secondary alcohol is immediately precipitated as an oil. The slight amount of alcohol left in solution can then be extracted, as by ether— and further dilution or continued extraction does not cause hydrolysis of the alkyl sulfuric esters in the solution. These esters are relatively stable and do not readily hydrolyze below 100°. This led Brooks and Humphrey to state that since the original sulfuric acid contained not only H_2SO_4 but the hydrate

[80] *Chem. Rev. d. Fett.-u Harz-Ind.*, **5**, 27 (1898).

[81] *Petroleum*, **6**, 2301 (1911).

[82] B. T. Brooks and I. W. Humphrey, *J. Am. Chem. Soc.*, **40**, 822 (1918).

$H_2SO_4 \cdot H_2O$ or $\begin{matrix} HO \\ HO \end{matrix}\!\!>\!\!\begin{matrix} S-OH \\ O \end{matrix}\!\!<\!\!OH$, alkyl esters of both acids were probably formed, the ester of $H_2SO_4 \cdot H_2O$ being the one to hydrolyze most readily to give the free alcohol.

Since the per cent of unsaturated hydrocarbons in gasolines made by the thermal decomposition (cracking) of heavier oils, is relatively high, frequently being 40 per cent or more, the tendency in refinery practice is to use acid less dilute than 93 per cent acid, or by minimizing the proportion of acid used to selectively polymerize or remove the di-olefines present in such oils. It is well known that di-olefines are much more reactive and polymerize much more readily, than the simple olefines. The volume of such "cracked" gasoline now manufactured is so great that the quantity of amyl and hexyl alcohols which could be made from them without seriously affecting the amount of motor fuel of this kind, would exceed any conceivable demand for such alcohols for solvent or chemical purposes.

W. W. Clough and C. O. Johns have described a very pure grade of secondary amyl alcohol, pentanol-2, made from petroleum amylene. The boiling point is given as $119.2°$ (760^{mm}) and the specific gravity as 0.8088 at $20°/4°$. At $20°$ 100 grams of the alcohol dissolves 11.2 grams of water and 100 grams of water dissolves 4.2 grams of the alcohol.

It is possible that for the successful preparation of alcohols from the actylenes or other olefines higher in the series, the addition of hydrogen chloride followed by hydrolysis would be more effective, thus avoiding the excessive polymerization, which sulfuric acid causes with the higher olefines. Berthelot[88] showed that commercial amylene readily yields tertiary amyl chloride boiling at $85°$, and A. Michael[84] showed that n-butene and isobutene, and the amylenes all react readily with hydrogen chloride. This is a favorite reaction employed in the terpene series and usually proceeds quantitatively, each double bond adding hydrogen chloride. In the olefin series however, the

[88] *Ann.*, **127**, 72 (1863).
[84] *J. Prakt. Chem.*, **60**, 372 (1899).

addition of halogen acids (hydrogen chloride) has been very little studied with the higher members. It is probable that the reactivity of the higher members of the olefin series for hydrogen chloride falls off very markedly, as is the case with sulfuric acid, since Butlerow[85] showed that di-isobutylene is much less reactive to hydrogen chloride than isobutylene and the tri-isobutylene still less so.

LeBel described a method for separating the amylenes based on their capacity to unite with hydrogen chloride; those hydrocarbons which can form a tertiary halide by the addition of HCl do so most readily, i.e., at ordinary temperatures. Thus, trimethylethylene and unsymmetrical methylethylethylene react most readily, of the amylenes.

By direct chlorination of petroleum pentane (usually a mixture of normal pentane and isopentane) a mixture of monochloropentanes is obtained from which the corresponding alcohols or acetates can be made. By heating the mono-chloropentanes with sodium acetate in acetic acid at 190° to 200° the yield of amyl acetate is about 50 per cent of the theory.[86] The cost of chlorine and the difficulty of securing a good yield of monochlorides are unfavorable factors. The simple water hydrolysis of such alkyl chlorides does not appear to have been studied. Hexyl, heptyl and octyl alcohols can be made from unsaturated hydrocarbons by means of sulfuric acid, though with diminishing yields, and pure individual alcohols made in this way have not been described.

[85] *Ann.*, **189**, 51 (1877); *Ber.*, **12**, 1483 (1879).

[86] B. T. Brooks, D. F. Smith and Harry Essex, *Ind. & Eng. Chem.*, **10**, 512 (1918).

FACTORS DETERMINING CHEMICAL STABILITY

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The subject of chemical stability is one of primary concern to chemists, and great progress has been made in recent years in elucidating the factors which determine it. Since but little of the pertinent material has appeared in the English language, and since the significance for chemistry of much that has been done in physics has not been pointed out it has seemed worth while to prepare this review of work already published, and to include in it results of a study of the subject made by the writer during the past two years, in which he has had valuable assistance by Prof. W. C. Bray.

DEFINITION OF STABILITY

The term stability is used by chemists in several senses which it is desirable to distinguish. A substance is usually called unstable if it is hard to keep it from changing into something else. Ferrous hydroxide is unstable in the presence of the oxygen of the air, sodium is unstable in the presence of moisture, and yet each is quite stable by itself. On the other hand hydrogen peroxide, even when protected from external agencies, decomposes at least slowly, and is regarded as unstable. We see here, however, the importance of distinguishing different types of decomposition, for hydrogen peroxide is unstable with respect to water and oxygen, but not with respect to hydrogen and oxygen, as shown by the accompanying changes in free energy:[1] $H_2O_2 = H_2O + \frac{1}{2} O_2$, $\Delta F = -25,090$ cals.; $H_2O_2 = H_2 + O_2$, $\Delta F = +31,470$ cals. It cannot, therefore, decompose into its elements at ordinary temperatures, and is unstable only because water is more stable.

[1] Lewis and Randall, Thermodynamics, McGraw Hill Co., 1923.

In nitric oxide we have a substance which may appear quite stable in the sense that it may be kept indefinitely at ordinary temperatures, and yet pure NO could never be formed from its elements at 25° except at the expense of outside energy, for the free energy of the reaction $N_2 + O_2 = 2 NO$ is 20850 cals.[1]

But even this fact does not mean that the molecule of NO itself is unstable, but merely that the molecules N_2 and O_2 are together more stable, hence the above 20850 cals. do not measure the strength of the bond in the NO molecule, which is a question of primary concern.

Now questions of rate are exceedingly important, but they must not be confused with questions of equilibrium or thermodynamic stability, and in this paper only the latter will be considered. Moreover, we will take care to specify the products of decomposition whenever speaking of the instability of a substance.

The thermodynamic stability of a substance with reference to a specified decomposition is correctly measured by the free energy change accompanying it, but it is unfortunately the case that the free energies of relatively few substances have been determined. We shall have to depend, therefore, chiefly upon the heats of reaction. This can be done without very great danger when comparing reactions of the same type, and for others where the differences are considerable, since the heats and free energies do not often differ by large amounts. When neither of these quantities is known we may often still draw conclusions from the chemical behavior of substances and their methods of preparation.

DISCREPANCIES WITH ELECTROCHEMICAL THEORY

The most valuable guide the chemist has had in dealing with questions of stability is the electrochemical theory first hinted at by Davy and later developed by Berzelius. Although modern discoveries have made it necessary to alter the conceptions of Berzelius, they have given us a theoretical basis still better adapted to the essentials of the Berzelian doctrine. A knowledge of the tendencies of elements to add or give up electrons, as correlated with the Periodic System, and the familiar "replacement series," is still indispensable in the education of the chemist. We

apply these ideas not only to determine the relative stability of binary compounds, but also of more complex compounds such as hydroxides, carbonates, double salts, etc., in relation to their dissociation products. Thus, sulfites are more stable than carbonates because, as we say, SO_2 is a more "negative" oxide than CO_2; similarly, $Cu(OH)_2$ gives off water at a lower temperature than $Zn(OH)_2$ because ZnO and H_2O are farther apart, in an electrochemical sense, than are CuO and H_2O.

Difficulties are encountered by the purely electrochemical theory, however, in the realm of organic chemistry, where the assignment of positive and negative valence numbers, or the statement that an electron has left one atom and gone to another, becomes, to say the least, far less reliable as a guide in questions of stability. Even in the realm of inorganic chemistry, when we seek to account for the great stability of molecules like N_2, H_2, and O_2, the simple electrochemical theory becomes almost useless. Considerations of this sort led to the theory of G. N. Lewis[2] that the valence electrons are not the exclusive property of the negative atoms but are shared by both atoms. The remarkable fruitfulness of this theory of the chemical bond, during the brief period since its publication, is well known. It is, however, more a theory of valence and of the nature of the chemical bond than of its strength, and it is evident that the latter topic is one of the utmost importance.

There are, moreover, certain other discrepancies with the electrochemical theory, as ordinarily applied, which appear not to have been discussed, and which serve to make evident some important factors affecting chemical stability. Thus, the nitride of a metal should be more stable the more positive the metal, but lithium nitride is stable whereas cesium nitride is not, although it takes 1.49 volts more to transfer an electron from lithium to nitrogen than from cesium, or 103.1 kg. cals., more per mol of nitride, a very large difference. Magnesium nitride is likewise more stable than barium nitride or sodium nitride, although magnesium is less "positive" than either of the other metals.

[2] G. N. Lewis, This Journal, **38**, 762 (1916); Valence and the Structure of Atoms and Molecules, A. C. S. Monograph, 1923.

Again, it has been shown by Bardwell,[3] in this laboratory, that hydrogen separates at the anode when CaH_2 is electrolyzed, and hence may be regarded as the negative element in the compound. Accordingly, the stability of the hydrides should increase, going from lithium to cesium, and from calcium to sodium, whereas the reverse is true.

With carbides also, although the data are very incomplete, the more stable compounds are apparently formed with the less positive metals higher in the groups, and with the less positive elements, in group 2, rather than those in group 1. In short, if we were making an electrochemical or "replacement" series, using the above compounds as the basis, we would not duplicate the ordinary series obtained by consideration of the more familiar salts of the metals. The fact that the discrepancies obviously

TABLE 1

Heats of formation of alkali halides in kilogram calories

	F	Cl	Br	I
Li..........................	120	97	87	71
Na..........................	111	99	90	76
K..........................	109	105	97	85
Rb..........................	108	105	99	88
Cs..........................	107	106	101	90

are associated in part with low atomic number on the part of both constituents suggested that relative sizes of the component atoms in a compound might prove to be a factor of general importance in determining stability.

We have complete data for the heats of formation of the alkali halides, which are certainly near enough to their free energies of formation to indicate their relative stabilities. Table 1 gives values in round numbers in kilogram calories,[4] which show that the fluorides furnish another exception to the usual electrochemical order. It should be noted, further, that although the other three series show the familiar order the rate of change is very dif-

[3] Bardwell, This Journal, **44**, 2499 (1922).
[4] Cf. Landolt-Börnstein Tabellen.

ferent for the other halides, the chlorides approaching the fluorides.

The smallest alkali metals show a similar preference for oxygen, as shown in table 2, but this becomes negligible with sulfur. Unfortunately, data for the selenides and tellurides are too meager to serve as evidence.

The compounds of the metals of group 2 show similar discrepancies, as shown in table 3, although the maximum stability in the cases where the electrochemical order does not hold is at calcium rather than beryllium, while the chlorides and iodides,

TABLE 2

Heats of formation in kilogram calories

	Li	Na	K	Rb	Cs
Oxides......................	142	101	87	84	83
Sulfides....		90	87	87	87

TABLE 3

Heats of formation of compounds of alkaline earth metals

	F	Cl	I	O	S	Se
Be........................		113		136		
Mg.................	209	151	85	144	79	
Ca....................	239	190	141	152	111	78
Sr........................	235	196	142	140	110	78
Ba.........	223	197	148	126	102	70

on the other hand, increase regularly according to electrochemical theory.

Facts such as the above, contradicting the simple electrochemical theory so much relied upon by chemists, invite the application of certain recent developments in physics which are of significance in bringing to light various factors which influence chemical stability.

IONIZING POTENTIALS

The basis of the "replacement series" is the ease with which elements lose or gain electrons. As we now usually say, sodium is a very positive metal because it has a loosely held outer electron which readily passes to a chlorine atom, where it is tightly held,
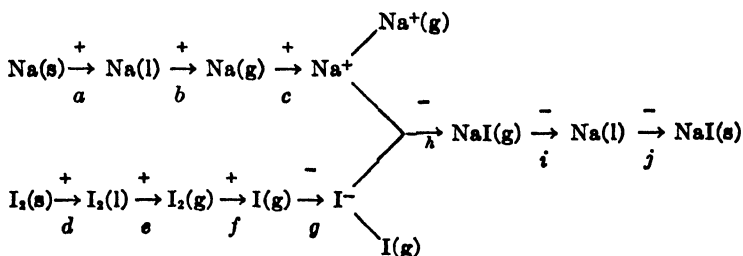
completing a stable octet. The resulting positive sodium ion and negative chlorine ion are then held together in the crystal by electrostatic attraction. In potassium the outer or valence electron is more loosely held, so that potassium chloride is formed with greater evolution of energy than is sodium chloride. The ease with which electrons are lost or gained has been measured directly as ionizing potential, or calculated indirectly from spectroscopic data.[5] Table 4 gives values for the metals of groups 1 and 2, which illustrate their harmony with the familiar electrochemical explanations of chemical phenomena, such as are associated with the "replacement series."

TABLE 4

Ionizing potentials, volts

Li	5.37	Be	>Mg	Be$^+$	?
Na	5.12	Mg	7.61	Mg$^+$	14.97
K	4.32	Ca	6.09	Ca$^+$	11.82
Rb	4.16	Sr	5.67	Sr$^+$	10.98
Cs	3.88	Ba	5.19	Ba$^+$	9.96

MELTING AND BOILING POINTS, HEATS OF DISSOCIATION OF ELEMENTARY MOLECULES, ETC.

The ionizing potentials represent the energy involved in removing electrons from gaseous atoms, and hence do not represent all of the energy of formation of a compound like solid NaI from solid sodium and solid iodine. Let us divide this reaction into a series of steps, as has been done by Born[6] and others, as follows:

$$\begin{array}{c}
\text{Na(s)} \xrightarrow{+}{a} \text{Na(l)} \xrightarrow{+}{b} \text{Na(g)} \xrightarrow{+}{c} \text{Na}^+ \diagup \text{Na}^+(g) \\
\diagdown{\ \ } \\
\diagup \xrightarrow{-}{h} \text{NaI(g)} \xrightarrow{+}{i} \text{NaI(l)} \xrightarrow{+}{j} \text{NaI(s)} \\
\text{I}_2\text{(s)} \xrightarrow{+}{d} \text{I}_2\text{(l)} \xrightarrow{+}{e} \text{I}_2\text{(g)} \xrightarrow{+}{f} \text{I(g)} \xrightarrow{-}{g} \text{I}^- \diagdown \text{I(g)}
\end{array}$$

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[5] See summary by Payne, Proc. Nat. Acad. Sci., **10**, 323 (1924); also Bul. Nat. Res. Council, **9** (1924).

[6] Born, Ber. deut. phys. Ges., **21**, 13, 533, 679 (1919).

The signs indicate the increases and decreases in heat content, ΔH, of the several steps of the process. Since the total ΔH is negative for a stable substance (formed with evolution of heat), the stability will be greater the smaller the (positive) values of steps a, b, c, d, e, and f, and the larger the (negative) values of steps g, h, i, and j. Where we do not know the heats of fusion and of vaporization we can use the melting and boiling points to make rough comparisons for different substances between the magnitudes of ΔH for the steps a, b, d, e, i and j. Thus, lithium melts and vaporizes at much higher temperatures than potassium, so that larger values for steps a and b for lithium tend to make all lithium compounds less stable than the corresponding potassium compounds.

On the other hand, where one compound is less fusible and volatile than another, steps i and j have larger values and tend to make the former compound more stable. We will return to a consideration of these factors in the later discussion of various examples.

We see that differences in the heat of dissociation of a gaseous molecule into atoms, step f, also influences the total heat of the process. Thus the higher stability of Cl_2 as compared to $I_2(g)$ with respect to their atoms tends to reduce the comparative stability of chlorides.

THE SIZE OF ATOMS AND THE ENERGY EVOLVED WHEN COMPOUNDS ARE FORMED FROM GASEOUS IONS

Little attention has been paid until recently to step h in the above scheme, the energy involved in the union of the gaseous ions to form the compounds. Born and Landé[7] have published a calculation of the electrostatic potential of the ions in the crystal lattice. They assume that the ions in the lattice are held in equilibrium position by the force of electrostatic attraction, obeying Coulomb's law, balanced by that of repulsion, which varies with the distance r by a higher inverse power law. The potential

[7] Born and Landé, Ber. d. deut. Physik. Ges., **19**, 210 (1918); Born, ibid., **21**, 13 (1919).

energy, u, converted into external energy as N ions of each kind come together is given by the expression:

$$u = N \left(\frac{a}{r} - \frac{b}{r^n} \right)$$

The constant a is 13.94 e^2, where e is the elementary charge, and the value of b is got from the relation that $(du/dr) = 0$ in the quilibrium position. This gives $b = \frac{ar_0^{n-1}}{n}$, where r_0 is the lattice constant. The compressibility depends likewise on du/dr, and in terms of the above assumption is:

$$\beta = \frac{9\,r_0^4}{a(n-1)}$$

The value of n necessary to give agreement with the experimental values is approximately 9 (from 7.75 to 9.6) for the halides of

TABLE 5

Lattice energies from Born and Landé's theory

	F	Cl	Br	I
Li..........................	231	179	167	153
Na..........................	220	182	168	158
K..........................	210	163	155	144
Rb..........................		144	140	138
Cs..........................		156	150	141

the various alkali metals except lithium, where it is about 5. The lattice constant is related to the density, ρ, and the atomic weights μ^+ and μ^-. For the complete dissociation of the crystal into gaseous ions the heat then becomes $490 \left(\frac{\rho}{\mu^+ + \mu^-} \right)^{\frac{1}{3}}$ kgm. cals. for lithium halides and $545 \left(\frac{\rho}{\mu^+ + \mu^-} \right)^{\frac{1}{3}}$ for the other alkali halides. The values so calculated by Born are given in table 5.

It will be noted that the smaller the ions the greater the decrease in potential energy when they unite, and hence the greater the heat of formation from the gaseous ions.

Latimer[8] has criticised the assumption that the field of force about the ions can be calculated on the basis of a rigid structure to the neglect of the changes in potential and kinetic energy of the electrons in each ion. Of course, a purely empirical equation for the potential of the ions in a crystal should, if correct, make possible the calculation of both compressibility and heat of ionization, but the fact that such an equation fits the compressibility data does not make it reliable for calculating heat of ionization because of the wide extrapolation involved. We cannot, therefore, place great reliance in the values in table 5. Nevertheless, there can hardly be any doubt that they are correct in indicating that the heat of ionization increases with decreasing atomic size. Almost any reasonable assumption regarding the laws of force about the ions would give this result, moreover, we know from the ionizing potentials, given in table 4, that the energy require to dissociate an electron increases with decreasing atomic size, and it can hardly be otherwise when a negative ion is substituted for an electron.

The total energy of formation is known, and all of the steps in the process as outlined above except the electron affinity of the halogens, step *g*, and the energy of combination of the gaseous ions, step *h*. The lattice energies could therefore be calculated from thermodynamic data alone if the electron affinities of the halogen atoms were known. Franck[9] has given an interpretation of the spectrum of iodine whereby the electron affinity of the iodine atom is 59.2 kg. cals. Born and Gerlach[10] have pointed out the discrepancy of 21 kg. cals. between this value and the one derived from lattice energies, and concluded that the lattice theory must be altered. More recently, however, Oldenberg[11] has shown this interpretation to be hardly tenable.

Grimm[12] in several comprehensive papers on the Born theory has also attempted to calculate this affinity from the data for the

[8] Latimer, J. Am. Chem. Soc., **45**, 2803 (1923).
[9] Franck, Z. f. Phys., **5**, 428 (1921).
[10] Born and Gerlach, Ibid., **5**, 433 (1921).
[11] Oldenberg, Z. f. Physik., **25**, 136 (1924).
[12] Grimm, Z. f. phys. Chem., **102**, 113, 141 (1922).

formation of the hydrogen halides, assuming that the concordant ionization potentials determined by Foote and Mohler,[13] Knipping,[14] and Mackay[15] represent the splitting of the molecule into hydrogen and halide ions. This, however, is not the case, as Mackay attributed this ionization to the removal of an electron, forming ions of the type HCl^+, and Barker and Duffendack[16] have adduced good evidence in support of this interpretation.

We have, therefore, no sufficient basis for the calculation of lattice energies apart from the somewhat questionable assumptions of Born and Landé. Nevertheless, it can be shown that the lattice energy increases as we go from the larger to the smaller elements, for the difference in lattice constants between the same halide of two alkali metals eliminates the electron affinity of the halogen. This sort of study has been made by Born and his co-workers, and more recently in very thoroughgoing fashion by Grimm.[17] It seems desirable, however, to make a more critical selection of some of the fundamental data used.

For the heats of vaporization of the alkali metals we have fairly concordant values calculated from the vapor pressures for all the metals except lithium.[18] (These do not agree well with the values derived by von Wartenberg and Schultz[19] from a modified Troutons' rule.) I have calculated a value for lithium from my generalization regarding the entropy of vaporization,[20] assuming that the boiling point is 1500°. The alkali metals deviate increasingly from the rule for normal liquids as we descend the group from sodium to cesium, but the deviation with sodium is small, and for lithium is undoubtedly less, so that I have assumed a value between the value calculated from the sodium curve and the one from the curve of a normal liquid.

The values for the heats of fusion are from Landolt-Börnstein

[13] Foote and Mohler, J. Am. Chem. Soc., **42,** 1832 (1920).

[14] Knipping, Z. f. Physik., **7,** 328 (1921).

[15] Mackay, Phil. Mag., **46,** 828 (1923).

[16] Barker and Duffendack, Phys. Rev., **26,** 339 (1925).

[17] Grimm, loc. cit.

[18] Cf. Landolt-Börnstein Tabellen, also Scott, Phil. Mag., **47,** 32 (1924).

[19] von Wartenberg and Schultz, Z. f. Elektrochem., **27,** 568 (1921).

[20] Hildebrand, J. Am. Chem. Soc., **37,** 970 (1915); **40,** 45 (1918).

Tabellen except for lithium, which is obviously much too low, in view of the melting point of the element.   Table 6 gives the values used, together with their sums, the heats of sublimation, steps *a* and *b*, in our scheme.

The increase in heat content in kilogram calories when an electron is removed from an atom of alkali metal is got by multiplying the ionizing potentials (table 4) by 23.07, giving for Li, 126; Na, 118; K, 100; Rb, 96; Cs, 90.

⸢ The heats of fusion of the alkali halides are known in only four cases, and values for the others have been calculated by

TABLE 6

Heats of fusion, vaporization and sublimation of the alkali metals, kilogram calories

	Li	Na	K	Rb	Cs
Heat of fusion...................	0.8	0.6	0.6	0.5	0.5
Heat of vaporization.............	42.5	25.4	18.8	18.0	17.6
Heat of sublimation..............	43 3	26.0	19.4	18.5	18.1

TABLE 7

ΔH for (1) vaporization and (2) fusion for alkali halides

	F		Cl		Br		I	
	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
Li......................	54	8	37	5	36	4	37	4
Na......................	54	8	45	7	40	6	38	6
K.......................	43	7	41	6	39	6	38	6
Rb......................	40	6	39	6	38	6	37	6
Cs......................	36	6	37	6	37	6	37	5

assuming constancy of the ratio $\Delta H/T_{m.pt.}$.   The error thus introduced into our calculations cannot be very large, for the heat of fusion is but a small part of the whole heat of formation.   For the heats of vaporization we have data by von Wartenberg and by Ruff[11] and co-workers.   In the few cases where these are discordant Periodic relations have been considered in selecting the more probable value.   Table 7 gives the selected values.

From the above data it is possible to calculate ΔH when a gaseous

[11] Cf. Landolt-Börnstein Tabellen.

alkali ion replaces another from either the gaseous or solid halide. For example, we have:

REACTION	ΔH	CF. TABLE
(1) Li(s) + NaI(s) = Na(s) + LiI(s)	+5	1
(2) Li(g) = Li(s)	−43	6
(3) Na(s) = Na(g)	+26	6
(4) Li$^+$(g) + E$^-$ = Li(g)	−126	4
(5) Na(g) = Na$^+$(g) + E$^-$	+118	4
Adding		
(6) Li$^+$(g) + NaI(s) = Na$^+$(g) + LiI(s)	−20	
Further		
(7) LiI(s) = Li(g)	+41	7
(8) NaI(g) = NaI(s)	−44	7
Adding (6), (7) and (8)		
Li$^+$(g) + NaI(g) = Na$^+$(g) + LiI(g)	−23	

TABLE 8

-ΔH for replacement of gaseous alkali ions in solid halides by alkali ion of next higher atomic weight

REPLACEMENT	F	Cl	Br	I
Na$^+$ (g) by Li$^+$ (g)	29	23	22	20
K$^+$ (g) by Na$^+$ (g)	27	19	18	16
Rb$^+$ (g) by K$^+$ (g)	5	4	2	1
Cs$^+$ (g) by Rb$^+$ (g)	7	5	4	4

TABLE 9

·ΔH for corresponding replacement in gaseous halides

	F	Cl	Br	I
Na$^+$ by Li$^+$	25	33	28	23
K$^+$ by Na$^+$	15	14	17	16
Rb$^+$ by K$^+$	9	2	1	0
Cs$^+$ by Rb$^+$	3	3	3	3

Applying this process to the other cases we get the values in table 8 for −ΔH for the replacement of the gaseous alkali ion of one *solid* halide by the gaseous alkali ion of next lower atomic weight, and for the corresponding replacement in the *gaseous* alkali halides we get the values in table 9.

In these tables the effect of different ionizing potentials has been eliminated. It is evident that in all cases the ion of the lighter metal replaces the one of the heavier. This is the reverse of the order shown in the ordinary replacement series where the ionizing potentials obscure the effect of the different attraction between the ions. It will be noted that the change from K to Rb and from Rb to Cs has but little effect but that in going from K to Na the effect is large, and from Na to Li it is still larger. Moreover, the changes in table 8 are largest for the fluorides, diminishing regularly to the iodides, so that we see evidence that the greatest ionic attractions exist not only where the positive ion is smallest, but also with the smallest negative ion, that is, the heat of union is greatest for $Li^+ + F^-$.

It is evident that the affinity of a positive ion for an electron bears some relation to its affinity for a negative ion. Thus the difference in electron affinity between Li^+ and Cs^+ is 36 kgm. cals., while the differences between their affinity for the halide ions, according to the values in table 9, range from 42 to 54 kgm. cals. The same explanation evidently applies in both cases; just as the closer approach of the electron to the smaller ion evolves more energy, so likewise the closer approach of a halide ion to the smaller positive ion evolves more energy. This should be qualitatively true even though the law of force between the ions is quite different from the one assumed by Born and Landé.

This effect of size is very strikingly shown by the large value of ΔH for the replacement of $Li^+(g)$ by $H^+(g)$ in such a reaction as $H^+(g) + LiCl(g) = Li^+(g) + HCl(g)$. Taking the heat of formation of HCl as 22 kgm. cals., the heat of dissociation of H_2 as 84 kgm. cals.,[22] and the ionizing potential of hydrogen atoms as 13.5 volts,[23] and combining with values for Li and LiCl as was done in calculating the figures in table 9, we get the very large value of ΔH for the above reaction of -152 kgm. cals. Therefore $H^+(g)$ easily replaces $Li^+(g)$ from LiCl in spite of the fact that Li metal easily replaces H_2 from HCl.

[22] Langmuir, J. Am. Chem. Soc., **36**, 1708 (1914); **37**, 417 (1915).
[23] Cf. Bull. Nat. Res. Council, **9**, 112 (1924).

DISTORTION OF THE IONS AS A FACTOR IN THEIR ENERGY OF COMBINATION

Latimer has called attention to the energy involved in the distortion of the ion, and pointed out that this may be different in different combinations. It seems obvious that a given amount of distortion involves less energy change for the outer than for the inner electrons, and this is born out by the fact that the compressibility of the elements in any group of the Periodic System increases with increasing atomic weight. We may conclude from

TABLE 10

Percentage contraction upon formation from elements

	F	Cl	Br	I
Li...........................	66	44	34	15
Na...........................	62	44	34	17
K...........................	61	46	38	25
Rb...........................	55	46	39	27
Cs...........................		56*	50*	41*

* Crystal lattice different from the others.

TABLE 11

Differences in 100a for various halides

	F	Cl	Br	I
KX − LiX................	132	114	108	106
KX − NaX................	71	65	63	60
RbX − KX................		25	27	25

this that the energy of combination of the ions should be more closely related to the *percentage* contraction than to the actual contraction when the ions unite to form the molecule. We have no data upon this, but table 10, showing the percentage contraction upon formation of the solid halides from their *elements*, pointed out by Mr. H. E. Bent, of this laboratory, shows the close connection between this contraction and the heats of formation in table 1. The high value of LiF is particularly striking.

Objection may be made that the figures in this table depend upon the values assumed for the individual elements, which vary with temperature. We may avoid any such objection by con-

sidering only the distances a, between the atomic centers for the salts themselves.[24] Table 11 gives the excess in 100 a for the halide of one alkali metal over that of a lighter metal, representing the relative contractions.

It will be seen that a change in the halogen has no effect upon the differences between rubidium salts and potassium salts, but that in going from iodides to fluorides there is a marked contraction for sodium salts as compared with potassium salts, and a still greater relative contraction for lithium salts.

The problem of the relation between chemical stability, contraction upon formation and atomic compressibility has been the subject of extended investigations by T. W. Richards.[25] He has pointed out the different atomic volumes of the same element in the different halides, and has calculated the following internal pressures in kilogram per square centimeter necessary to account for the observed volumes: NaCl, 100,000; NaBr, 85,000; KCl, 65,000; KBr, 54,000. He points out that "as would be expected from the heats of formation, the average internal pressure in the bromides is less than that in the chlorides. On the other hand, the average internal pressure is greater in the sodium salts than in the homologous potassium salts, although the heats of formation show the opposite order." In place of the explanation for this apparent paradox given by Richards, I suggest that this pressure should be related not to total heat of formation, but to the heat of combination of the ions to form the solid indicated in table 8 and confirmed by the contractions in table 11, and in Richard's own values for the atomic volumes in the chlorides and bromides of sodium and potassium.

Turning again to the alkaline earth metals, table 3, we see evidences of the same factors as with the alkali halides. The closeness of approach, in the case of the fluorides and oxides, reverses the electrochemical series for calcium, strontium and barium, but not for beryllium and magnesium. This is probably due to the large difference in the ionizing potentials between

[24] Cf. The Structure of Crystals, Wyckoff, Am. Chem. Soc. Monograph, Chem. Cat Co., 1924.

[25] T. W. Richards, J. Am. Chem. Soc., **45**, 422 (1923).

magnesium and calcium, seen in table 4, which tends to preserve the electrochemical series.

The fact that the atoms in MgO actually are more distorted than those in CaO, in spite of the smaller heat of formation, is indicated by the figures in table 12 calculated from the densities ·of the solids. We may, therefore, conclude that the reaction $Mg^{++}(g) + O^{--}(g) = MgO(g)$ would actually give out more ·energy than the reaction $Ca^{++}(g) + O^{--}(g) = CaO(g)$.

HEAT OF HYDRATION OF GASEOUS IONS

Fajans[26] has discussed the theory of Born and Landé in connection with the heats of hydration of the gaseous ions. When a solid halide is dissolved in a large amount of water the heat of
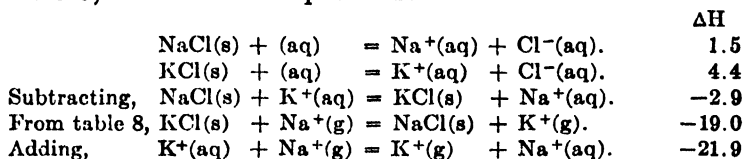
TABLE 12

	DENSITY		MOLAL VOLUME	Σ ATOMIC VOLUMES[*]	PER CENT CONTRAC- TION
	Metal	Oxide			
Mg............................	1.74	3.65	8.3	25	67
Ca..........	1.55	3.40	16.5	37	55
Sr............................	2.58	4.61	22.5	46	51
Ba............................	3.78	5 72	26 8	48	44

* Taking atomic volume of $O = 11.2$.

solution is equal to the sum of the heat of ionization into the gaseous ions and the heat of hydration of the gaseous ions. Since the first is known experimentally, if the values of Born are accepted for the second, the third can be calculated. It seems preferable, however, to proceed as in the former case, using thermochemical data only, and calculate the differences in heats of hydration of the gaseous alkali ions.

Using the following heats of solution, LiCl, -8.4; NaCl, $+1.5$; KCl, $+4.4$; RbCl, $+4.7$; CsCl, $+4.8$; and the replacement values in table 8, we have the equations:

$$\begin{array}{llll} & & & \Delta H \\ \text{NaCl(s)} + \text{(aq)} & = \text{Na}^+(aq) + \text{Cl}^-(aq). & & 1.5 \\ \text{KCl(s)} + \text{(aq)} & = \text{K}^+(aq) + \text{Cl}^-(aq). & & 4.4 \\ \text{Subtracting,} \quad \text{NaCl(s)} + \text{K}^+(aq) = \text{KCl(s)} + \text{Na}^+(aq). & & -2.9 \\ \text{From table 8,} \quad \text{KCl(s)} + \text{Na}^+(g) = \text{NaCl(s)} + \text{K}^+(g). & & -19.0 \\ \text{Adding,} \quad \text{K}^+(aq) + \text{Na}^+(g) = \text{K}^+(g) + \text{Na}^+(aq). & & -21.9 \end{array}$$

[26] Fajans, Ber. d. deut. phys. Ges., pp. 539, 549 (1919).

We see that the heat of hydration of $Na^+(g)$ is 22 kgm. cals. greater than that of $K^+(g)$. By carrying out the same process with all the alkali metals we get the values shown in table 13, with the values of the heats of ionization of the gaseous chlorides from table 9 repeated for comparison.

If the differences in heats of ionization are calculated from the heats of solution of the other halides identical figures with those from the chlorides are obtained.

The table also gives for comparison the corresponding figures for the replacement of $Li^+(g)$ by $H^+(g)$ both in solution and in the gaseous chlorides. The heat of hydration of $H^+(g)$ is seen to be 118 kgm. cals. greater than that of $Li^+(g)$. The smaller the ion the greater the heat evolved in union with water, as well as in union with an electron or with a halide ion. The effect

TABLE 13

$-\Delta H$ for differences in heats of hydration of gaseous ions

	REPLACEMENT				
	Li+ by H+	Na+ by Li+	K+ by Na+	Rb+ by K+	Cs+ by Rb+
In solution....................	118	33	22	4	5
In gaseous chlorides..............	152	33	14	2	3

of this is seen in the well known hydration and high solubility of the halides of lithium except the fluorides, where the high affinity seen in table 8 opposes the hydration. Thus, according to our figures, the difference between the compounds of $Li^+(g)$ and $Cs^+(g)$ is 68 kgm. cals. for the fluorides, 64 for the hydrated ions, and 41 for the iodides. Correspondingly, F^- holds Li^+ in preference to water, but I^- does not, so that LiF is insoluble while CsF is very soluble. On the other hand water removes both Cs^+ and Li^+ from I^-, hence both CsI and LiI are quite soluble.

Fajans has given values for the absolute values of the heats of hydration of the ions, but these depend upon the assumption that the absolute electrode potential of the calomel electrode is given by the capillary method, which is only approximately true, and also neglect the fact that electrons in the gaseous state are not the same as electrons in a metal. This error has been pointed

out to me by Professor Latimer, who will deal with this phase of the problem in a paper now in preparation. There has also been some confusion in the published work in this field between heats and free energies which must be avoided in the future development.

EFFECT OF VALENCE AND ATOMIC SIZES

In going from an element in group 1 to the one following it in group 2, as from sodium to magnesium, or from potassium to calcium, there is little change in the equivalent heat of formation of the fluoride, but with the oxides there is a marked increase

TABLE 14

Equivalent heats of formation. Effect of valence

	FLUORIDES	OXIDES	NITRIDES
Li.................................	120	71	16.5
Be.................................	?	68	Stable
Na.................................	111	50	Not stable
Mg.................................	105	72	20
K.................................	109	44	Not stable
Ca.................................	119	76	19
Cs.................................	107	42	Not stable
Ba.................................	111	63	25

except in the first row. With the nitrides the effect is still more marked, as shown in table 14. Since the elements in group 2 are less positive than those in group 1, this difference is contrary to simple electrochemical theory, and seems rather to be connected with the relative numbers and sizes of the atoms forming the compounds. In Na_3N we have three large atoms surrounding a small central one. Although the bond is doubtless very polar, it is screened by the sodium atoms so that its field cannot operate successfully to build up a stable lattice. The nitrides of the bivalent metals of group 2, however, contain twice as many nitrogen atoms, and the metallic atoms are smaller, so that the screening of the bond by the metallic atoms is impossible, and a stable lat-

tice can be built up. The phosphorous atom, although less negative than the nitrogen atom, is larger, and hence gives more stable compounds with the alkali metals because, presumably, the central atom is less hidden than in the nitrides, and the bond can exert more outside attraction. From the same viewpoint the smallest metal of each group gives the most stable nitride.

The differences between groups 1 and 2 are less for the oxides, because there are fewer screening metallic atoms, although nearly negligible between Li_2O and BeO because of the small size of the lithium atom. The differences practically disappear with the fluorides.

A further effect of size is seen in the increase in the number of oxygen atoms that can be accommodated about the alkali atom as the latter gets larger, leading to the highest and most stable, peroxides being at the bottom of group 1, although the most stable oxide is at the top.

A similar effect of valence is evident in the difference between the stabilities of the oxides and fluorides (or chlorides) of the polyvalent metals. Thus we have V_2O_5, CrO_3 and Mn_2O_7, but the corresponding chlorides and fluorides have never been prepared, in spite of the fact that fluorides are generally more stable than oxides. Likewise we have K_2CrO_4 and $KMnO_4$ but as yet no K_2CrF_8 or $KMnF_8$. In the latter the coördination number would have to be double what it is in the former, due to the difference in valence between oxygen and fluorine, and such a high coordination number as 8 is very rare. We do find it in RuF_8 and OsF_8, where the central atom is larger, just as we have the normal number of 4 exceeded in the case of periodic acid, K_5IO_7, but not with perchloric acid, $HClO_4$. Although iron is a baser metal than ruthenium or osmium, it is too small to show so high a coördination number as 8, so that there is no FeF_8.

INSTABILITY OF UNIVALENT COMPOUNDS OF GROUP 2

It has been difficult or impossible to prepare univalent compounds of the alkaline earth elements.[17] From the standpoint of

[17] Wöhler and Rodewald, Z. anorg. chem., 61, 54 (1909).

ionizing potentials this has appeared paradoxical, for the electrons do not come off in pairs. The removal of the second electron requires, as shown in table 4, about twice the potential required for the removal of the first electron. Therefore, a bivalent gaseous ion of calcium would remove an electron from a gaseous atom, as shown by the equation: $Ca^{++}(g) + Ca(g) = 2Ca^{+}(g)$, with an energy of 5.73 volts, or 133 kgm. cals. This large energy value, taken by itself, would indicate that univalent compounds should be quite stable with respect to the metal and bivalent compound, whereas, as a matter of fact, the reaction $Ca(l) + 2CaCl_2(l) = 2CaCl(l)$ occurs only with great difficulty at high temperatures, and $CaCl(s)$ is unstable at lower temperatures. The explanation of this apparent paradox seems to lie, at least partly, in the large energy previously shown to be involved in the combination of ions. This energy is evidently greater than the energy involved in the removal or addition of electrons. If we make the plausible assumption that this would hold true in group 2 also, then, since ΔH for the reaction $Ca^{++}(g) + E^- = Ca^{+}(g)$ is -273 kgm. cals.; ΔH for the reaction $Ca^{++}(g) + Cl^-(g) = CaCl^+(g)$ should be still larger, say $-(273 + x)$ cals.; also since ΔH for $Ca^{+}(g) + E^- = Ca(g)$ is -140 cals., ΔH for $Ca^{+}(g) + Cl^-(g) = CaCl(g)$ should be larger, $-(140 + y)$, and likewise for $CaCl^+(g) + Cl^-(g) = CaCl_2(g)$, say $-(140 + z)$, but y and z should both be made much less than x. By combination of the above equations we get ΔH for the reaction $2CaCl(g) = Ca(g) + CaCl_2(g)$ to be $-(x + z - 2y)$ which will be negative, and hence the CaCl relatively unstable, if $(x + z) > 2y$, which might easily be the case if our assumptions are true regarding the relative magnitudes of x, y and z. The corresponding reaction between solids, of course, introduces other factors, but the above discussion at least shows that the great stability of $2Ca^{+}(g)$ with respect to $Ca(g) + Ca^{++}(g)$ does not necessarily require that $2CaCl(s)$ should be stable with respect to $Ca(s) + CaCl_2(s)$. This explanation avoids the necessity of making the assumption, contrary to the ionizing potentials, of any pairing of the electrons in the calcium atom, although not denying its possibility in the

halide molecules.[28]   It is interesting to observe that CaCl would be what G. N. Lewis has called an "odd molecule," having an odd number of electrons.   Such molecules have but a rare existence, tending to pair unless oxidized or reduced.   We see this pairing in the case of mercurous ion, Hg_2^{++}, which is thus rendered capable of stable existence.   We might expect some tendency to pairing in CaCl, which may cause it to assume some other than the sodium chloride lattice.   The fact that it is colored is significant.

Other cases where a lower compound is stable with respect to higher compound and metal, as $FeCl_2$ with respect to Fe and $FeCl_3$, are mostly cases where the atom has a variable kernel. Lack of the required data makes their discussion at this time premature.

TABLE 15

	MgF$_2$	CaF$_2$	BaF$_2$	PbF$_2$	PbCl$_2$	PbBr$_2$	ZnS	CdS	HgS
m.pt...............	910	1360	1280	840	500	380	1850	1750	1450
$-\Delta H$...............	209	239	223	108	86	64	43	34	11

MISCELLANEOUS EXAMPLES

In addition to the numerous cases discussed in the foregoing paragraphs, several others may be cited that serve to illustrate well certain of the factors involved in stability.   We have seen that the energy with which gaseous ions are attracted to each other is a factor of fundamental importance.   Now the same forces responsible for this are in general responsible for building up a stable crystal lattice, one which resists melting and vaporization.   We may note a certain parallelism between the lattice energies of the alkali halides, table 9, and their melting and boiling points.

Dr. W. Westwater has traced this connection for a large number of substances.   Table 15 gives a few examples.   It is noteworthy

that one of our best refractories, ThO_2, has both the highest heat of formation and the highest melting point of the Group 4 oxides.

A particularly striking case of the stabilizing effect of large crystal forces is seen in comparing CO_2 and SiO_2. We may assume that the small size of the carbon atom favors the stability of the former, while the more electropositive character of silicon favors the latter. In order to eliminate these effects so far as possible, we give, in table 16, the ratio of the equivalent heats of formation of oxides to chlorides for these elements and the six preceding. We see that the stability of the oxide as compared with the chloride is *greater* for Li, Be and B, than for Na, Mg and Al, respectively, but that it is *less* for C than for Si. We may assume that for SiO_2 *gas* the figure would be about 1 instead of 1.53, and that the excess of the latter is to be attributed to the large heat of sublimation of solid SiO_2.

TABLE 16

Li........... 0.73	Be.......... 1.34	B........... 1.51	C........... 1.26
Na........... 0.51	Mg......... 0.95	Al.......... 1.17	Si........... 1.53
Ratio....... 1.43	1.41	1.29	0.82

We may expect, similarly, a large heat of formation of SnF_4 compared with $SnCl_4$, because the former is a solid with a high melting point, while the latter is a volatile liquid. This heat has never been measured, but since ΔH for SiF_4 is nearly twice ΔH for $SiCl_4$, we may expect that ΔH for SnF_4 would be *more* than twice as great as ΔH for $SnCl_4$ (140) or more than 280 cals.

We may recall here the relatively high stability of the hydride and carbide of lithium, mentioned in the opening paragraphs, and note that this is susceptible to the same explanation as has already been given for the compounds with the other elements with small kernels. It is interesting to find that just as oxygen tends to give stable peroxides with large atoms, on account, apparently, of the disparity in atomic volume, so carbon tends to give acetylides in groups 1 and 2 rather than simple carbides. It is the carbide of the smallest element only in group 2, Be_4C_3, that gives methane with water rather than acetylene.

The increasing stability in going from HI to HF is not surprising in the light of ordinary electrochemical considerations, but even here we can see the effect of the small size of the hydrogen and fluorine atoms when we note that the difference in $^-\Delta H$ between HF and HI is 32 kgm. cals., while between CsF and CsI it is only 17 kgm. cals. This same factor doubtless gives H_2O and exceptionally high stability compared with H_2S ($^-\Delta H$ for the gases, 58.3 and 2.7 respectively) and NH_3 likewise with respect to PH_3. There is no such difference between Na_2O and Na_2S, between Ag_2O and Ag_2S, and Cs_2S is even more stable than Cs_2O (cf. table 2).

The preference of atoms of small size for each other, evident throughout this paper, may be cited in explanation of the fact that the chemistry of carbon is chiefly an account of its combinations with hydrogen, nitrogen and oxygen, elements with small atomic kernels.

The material in this paper should serve to emphasize the importance of a determination of one of the two unknown quantities still remaining in the steps into which the formation of a compound has been divided, viz., the electron affinity of the halogen atoms or the energy of combination of the gaseous ions. The most promising attack upon the latter problem seems to be offered through the study of band spectra.

CORROSION OF IRON

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The selection of material for a review on corrosion is complicated by the breadth of the field, the variety of phenomena encountered and the conflict of published opinion and theory. It therefore seems best to confine the discussion to certain features which have wide application and which have excited recent experimental research rather than to attempt anything in the nature of a complete bibliography of the subject.

ELECTROCHEMICAL THEORY

According to electrochemical concepts of corrosion, the reaction takes place through a cell between two surfaces. At the anodic surface the metal goes into solution, while one or more corresponding reactions go on simultaneously at the cathode, the current passing from anode to cathode through the solution and back to the anode through the solid.

The electrochemical theory was first developed to explain the phenomena when two metals of different solution potentials are in contact, but it was evident that the same sort of action could occur between two surfaces on a single piece of metal. Working along this line, the ferroxyl indicator test was widely used to illustrate differences in the solution potentials exhibited at different points on the surface of a metal.

The general applicability of this theory has been attacked on the ground that many cases of corrosion might be explained as direct chemical combination of oxygen with the metal, even though other cases necessitated the introduction of electrochemical conceptions. The critics failed to recognize that there is no arbitrary distance over which the cell must act in order to classify the action as "electrochemical." Corrosion phenomena

between two separate pieces of metal in a solution, connected only externally are admittedly electrochemical, and the same is true for the action between a plated metal and the bare metal exposed by a pinhole in the plating. There is no reason for assuming that the action ceases to be electrochemical just because the anode and cathode areas are on the same piece of metal and may be closely adjacent. Indeed, these areas might well be contiguous molecules, and the corrosion would still be electrochemical.[1] Electrochemical action is now generally accepted as the fundamental explanation of corrosion phenomena at ordinary temperatures, even by those who formerly adhered to the theory of direct chemical attack or to that of colloidal catalytic action.

Many of the more important factors in corrosion can be predicted directly from its electrochemical nature. This can be shown by considering the simultaneous reactions occurring at the anode and at the cathode.

Anode reactions

Since metal dissolves at the anode, the two primary factors governing this reaction should be the solution potential of the metal and the concentration of metal ions in the solution adjacent to the surface. A potential for the half-cell

$$M, M^+$$

can be calculated directly from the normal potential of the metal and the metal ion concentration by the Nernst equation:

$$E - E_o = \frac{n}{RT} \ln \frac{1}{C}$$

Other things being equal, corrosion will be more rapid with metals of higher solution potential and with solutions where the metal ion concentration is low.

There are many apparent contradictions to this statement

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[1] R. J. McKay and B. D. Saklatwalla, Discussion at Detroit (1924), Meeting of Am. Electrochem. Soc.

because the "other things" are very seldom equal. As a matter of fact, solution pressure per se is frequently an unimportant factor due to supervening effects. Metals of very high potential like sodium and calcium do indeed "corrode" with great rapidity, but aluminum is generally more resistant than iron, although it has a higher potential. This case, and a great many others of the same nature, is explained by difference in the protective action of the corrosion products. Another apparent contradiction, the corrosive effect of concentrated solutions of ferric salts on iron, is readily explained by the oxidizing power of such solutions.

On the other hand although copper and gold are resistant metals they can be rapidly corroded in solutions where a complex ion forms and reduces the free metal ion concentration to an exceedingly low value—e.g., copper in ammonia and gold in cyanide solution.

Cathode reactions

The cathodic reduction may occur in many ways depending upon the corrosive conditions. For example, if iron corrodes in a solution of copper salt and metallic copper plates out, the cathode reaction is copper ion giving metallic copper.

In most cases the cathode reaction is the liberation of hydrogen gas or the reaction of dissolved oxygen, or these two in parallel.

High hydrogen ion concentration assists both reactions, in accordance with the Nernst equation. When hydrogen gas is evolved, either as a gas or dissolved in the solution, the tendency to corrode is greater as the pressure on the gas diminishes. Thus hydrogen gas may be dissolved in dilute solution more readily than it can be evolved as gas bubbles at atmospheric pressure. The rate of hydrogen gas formation is decreased by overvoltage: a resistance which is a function of many variables such as the nature and surface of the metal, the composition of the solution and the geometrical shape of the surface. Overvoltage is a factor of primary importance in the acid corrosion of iron, zinc and other anodic metals, but it will not be treated in detail in this review.

The character of the cathodic reaction of oxygen is discussed in a later section.

Oxygen has long been recognized as an important factor in corrosion, but the many ways in which it determines the amount and character of corrosion are recent discoveries. The earlier theorists assigned to oxygen the rôle of oxidizing corrosion products such as ferrous hydroxide to a higher state. The full responsibility of oxygen for most natural corrosion was brought out by Walker[2] in his experiments which showed the corrosion of steel under water to be proportional to the concentration of oxygen dissolved in the water.

Corrosion can, of course, proceed in the complete absence of oxygen or other oxidizing agents. Thus iron will dissolve in hydrochloric acid, and will be appreciably corroded by water at high temperatures when the system is quite freed from oxidizing agents. Even at room temperature a slight corrosion occurs on iron in contact with deoxygenated neutral solutions.[3] However, of the total economic loss due to corrosion it is safe to estimate that over 90 per cent can be charged to the account of oxygen.

Nature of reaction

The method by which oxygen attacks metals has been explained by many theories. One which received wide acceptance was that the initial electrochemical reaction of a metal with water produced the metal hydroxide and hydrogen gas—and that the oxygen then oxidized the hydrogen gas to form water. The major obstacle to this theory was the well-known fact that dissolved oxygen gas does not react with dissolved hydrogen gas to form water. Unfortunately, the promulgation of this impossible process reacted to discredit the whole idea of electrochemical action.

This difficulty was removed by assuming that dissolved oxygen reacted with hydrogen in the atomic form, i.e., with "nascent" hydrogen which had been discharged at the surface. Such a concept has the marked advantage that it is readily presented by a logical and consistent series of reactions. In the

² Walker, Cederholm, Bent J. A. C. S., **29**, 1251 (1907).
³ Shipley and McHaffic, Can. Chem. Met., **8**, 121 (1924).

first and primary stage the metal goes into solution at the anode, and hydrogen ions discharge at the cathode, forming nascent hydrogen.

$$\text{At anode:} \quad Fe + 2 \oplus = Fe^{++}$$
$$\text{At cathode:} \quad 2H^+ = 2H + 2 \oplus$$
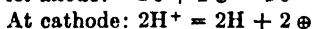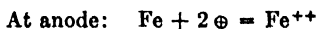
Atomic hydrogen is then removed either by the formation of hydrogen gas

$$2H = H_2$$

or by reaction with an oxidizing agent such as dissolved oxygen.

$$2H + \tfrac{1}{2}O_2 = H_2O$$

or by both reactions in parallel.[4]

While this formulation is now widely accepted, and is perhaps the simplest method of expressing the processes it is subject to the following objection. When applied to the corrosion of copper and of other metals cathodic to hydrogen, the idea that such metals will go into solution and plate out hydrogen is at first thought unreasonable. As a result, certain investigators in the past have felt compelled to discard the electrochemical theory when applied to copper, and have formulated other theories like those of direct oxidation to fill in the gaps thus created.

There is no real justification for such hesitance when we remember that the position of hydrogen in the electromotive series is determined by measurements of the potential of the half-cell, hydrogen ion against gaseous hydrogen. Now the primary reaction does not involve or imply gaseous hydrogen but produces hydrogen in an intermediate state referred to as "atomic" or "nascent." Therefore, although copper is cathodic to hydrogen in the special case where hydrogen gas is considered (and where the copper ion concentration is not abnormally low), it may legitimately be considered as anodic to hydrogen when the deposited hydrogen is removed by some oxidation reaction.

[4] Hydrogen peroxide may be formed as an intermediate product of the oxygen reaction (Bancroft, J. I. E. C., **17**, (1925) 336) but this possible step need not be introduced in considering the net result of the process.

To avoid the difficulty in visualization discussed above, the reaction of oxygen may be presented in an alternative manner.[6] Thus the cathode reaction, consisting of deposition of nascent hydrogen followed by the reaction of the hydrogen with dissolved oxygen to form water, gives as its net effect the disappearance of one mol of water (which ionized to produce the hydrogen ion), and of one-half mol of oxygen, and the production of two hydroxyl ions and of two positive charges.

$$H_2O + \tfrac{1}{2}O_2 = 2OH^- + 2 \oplus$$
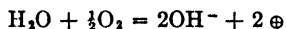
As a result, rather than picturing the discharge of hydrogen ions and their subsequent oxidation, the cathode reaction can be looked upon as the operation of an oxygen cell which produces hydroxide ions.

The choice between these two formulations is determined primarily by the relative ease with which they can be grasped. Either one is adequate if properly appreciated. Present usage favors the former, but the idea of an oxygen half-cell permits direct calculation of theoretical corrosion potentials and clarifies the consideration of the corrosion of "cathodic" metals.

It might be argued that the suggestion of an oxygen half-cell is a reversion to the theory of chemical action, which postulates direct reaction between oxygen and the metal. There is, however, one vital distinction between the chemical and electrochemical theories which is in no way vitiated by the new concept. By the former, corrosion can occur only at the place where oxygen reacts—by the latter, the metal may go into solution at a point separated from the oxygen by a finite distance. So many corrosion phenomena have been observed where the corroding metal and the corroding agent were not in contact that direct chemical action cannot possibly be regarded as a theory of universal application.

Rate of reaction

The rate of corrosion by dissolved oxygen is a function of so many variables that no single factor can be selected as deter-

[6] Whitman and Russell, J. Soc. Chem. Ind., 43, 1931 (1924).

mining all cases. Often the initial tendency to corrode is so slight that the rate of reaction is necessarily slow, as in the attack of noble metals by oxygen in distilled water. In most of the important cases, however, there exists so great a tendency to react that the rate is limited, not by chemical factors, but by physical ones.

Wilson[6] has stated the case for the corrosion of iron and steel in natural waters which contain dissolved oxygen. Iron has a high tendency to corrode under such conditions, the theoretical corrosion potential in neutral water at room temperature saturated with air being calculated as 1.74 volts.[7] The reactivity is therefore so great that corrosion may be considered to occur instantaneously when oxygen reaches a surface which is in effective electrochemical contact with the corroding metal. Under such conditions the only thing preventing a very rapid corrosion is the fact that the corroding agent, dissolved oxygen, cannot be supplied to the cathode rapidly enough to maintain the high corrosion rate.

It is evident that, if the corrosion rate is limited by the rate of supplying oxygen, the controlling factors are physical rather than chemical. This view is supported by numerous observations, one of the most convincing of which is that steels and irons of widely differing chemical composition show the same corrosion losses when kept under water for long periods. The importance of physical factors external to the metal itself is predominant in such cases.

The rate at which dissolved oxygen can be supplied to a surface in effective electrochemical contact with the corroding metal is, like so many other rate phenomena, a problem of diffusion. It is therefore determined by the diffusion potential and by the diffusion resistance. If the main body of the solution around the metal contains dissolved oxygen to the extent of perhaps 5 cc. per liter, and the oxygen concentration is zero at the cathode surface (because reaction there is practically instantaneous) the diffusion potential is 5 minus 0 = 5 cc. per liter. Other things being equal,

[6] J. I. E. C., 15, 127 (1923).
[7] Whitman and Russell, loc. cit.

and in the absence of side reactions such as hydrogen gas evolution, the corrosion rate should therefore be directly proportional to the oxygen concentration in the solution. The experiments of Walker[3] confirm this view. Wilson makes use of this proportionality in deriving a "specific corrosion rate" in order to compare the rates obtained under different conditions where the oxygen content of the solution varied. His "specific" rate is the actual rate of corrosion divided by the oxygen concentration of the solution.

The other diffusion factor—"diffusional resistance"—is somewhat more complicated. In the simplest case, where a metal corrodes without building up films of corrosion products or costings from the solution, the diffusional resistance is due only to the quiet surface film of solution against the metal. This liquid film is sometimes spoken of as a "friction skin" of fluid, and is always present when two phases are in contact. The effective thickness of such films under definite conditions is known for some cases from studies of heat transfer, fluid friction and related processes. In a few instances it has been possible to correlate corrosion rates with the rate of oxygen diffusion calculated from the diffusivity of oxygen through water, the diffusion potential, and the effective film thickness as determined by such indirect methods.[9]

In most practical cases of corrosion, however, solid films form on the surface of the metal and influence the rate of diffusion. This brings up the whole question of solid coatings, a subject of utmost importance in corrosion which is still largely a matter of speculation. Certain types of corrosion products, such as the rust formed on iron in distilled water, seem to have very little effect on the corrosion rate because of their porous non-adherent nature. This statement deserves the qualification that the initial rate, before rust has formed on the surface, is usually high, but once the film has attained appreciable thickness subsequent increases in thickness do not have any marked effect. Now since the very presence of such rust should increase the thickness of the

[3] Walker, Cederholm and Bent, loc. cit.
[9] For example of such calculation see Wilson, loc. cit.

fluid "friction skin" this means that the dissolved oxygen, as such, does not have to diffuse completely into the underlying metal in order to find an effective cathode surface. Such a view is substantiated by the observation that films of rust on submerged iron are highly oxidized on the outer surface, but are in the ferrous form on the side in contact with the metal. It seems probable that the oxygen reaches an "effective cathode area" in electrochemical contact with the corroding metal within the rust film itself. The exact mechanism is unknown, but may well involve an oxidation of ferrous to ferric rust in the layer of corrosion products.

It is well known that natural waters vary greatly in their corrosive action on metals. In most cases the effect is not attributable directly to acidity and the formation of hydrogen gas, although acidity may have a vital influence on the character and amount of solid coating formed on the metal. Thus, experiments[10] in a soft natural water where the pH was varied from 9.5 to 5.0 by adding sodium hydroxide or hydrochloric acid, showed no change in corrosion rate with pH value within these limits. Conversely, the corrosiveness of the water supply of the City of Baltimore has been greatly decreased by the addition of sufficient lime to precipitate carbonate scale on the pipes.[11] In the soft water experiments the addition of alkali up to a pH of 9.5 did not cause scale formation, while with the Baltimore water supply the results were quite the opposite.

Additions of alkali to give a pH higher than 9.5 to the soft water reduced corrosion, the rate diminishing progressively as pH was increased. However, it has been observed that the initial corrosion rate in dilute alkali is just as rapid as the initial rate[12] with neutral water. The effect of alkalies is therefore to build up protective films which reduce corrosion. This is of particular importance, since it contradicts the earlier opinion that alkalies were effective retarders because they cut down the concentration of hydrogen ions necessary for corrosion. As a matter

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[10] Whitman, Russell, Altieri, J. I. E. C., **16**, 665 (1924).

[11] Baylis, Chem. Met. Eng., **32**, 874 (1925).

[12] Speller and Texter, J. I. E. C., **16**, (1924) 393.

of fact, the theoretical corrosion potential in dilute alkali when iron is corroding is just as great as it is in natural waters, and the "insufficient hydrogen-ion" theory had no theoretical basis.

The action of protective films is intimately connected with oxygen diffusion since they set up barriers aganst the free access of oxygen to an effective cathode surface. They may be considered as more or less effective insulators preventing electrochemical contact between the metal and the corroding agent in the solution.

Localization of corrosion

Aston,[13] investigating the effect of wet rust on a surface, found that the metal beneath this rust was anodic and explained this as due to the low concentration of dissolved oxygen under the rust. Since that time many similar experiments have been performed, the work of Evans[14] being particularly noteworthy. Evans, studying the corrosion under a drop of water on a clean surface of steel, noted that the outer ring of metal under the drop was relatively unattacked, but that corrosion proceeded rapidly under the center of the drop and formed a pit there. He explained this as caused by differences in the concentration of oxygen dissolved in the water at the outer surface of the drop and in the center. Since the oxygen supply for corrosion came from the air by a process of dissolving in the water, the surface of the drop should be most nearly saturated and the interior should be most deficient in oxygen.

Several explanations of the phenomena have been suggested, each of which has considerable basis for argument. It is probable that the following series of steps, combining certain features of each, approximates the actual mechanism.

Initially the oxygen concentration throughout the drop is uniform and the tendency for localized corrosion is haphazard. As soon as an appreciable amount of oxygen has been consumed, however, the oxygen concentration is lower at the center and remains so during the rest of the experiment. Now a difference of

[13] Aston, Trans. Am. Electrochem. Soc., 29, 449 (1916).
[14] U. R. Evans, J. Soc. Chem. Ind., 43, 15 T (1924).

oxygen concentration at two points does not mean per se that the corrosion will be localized at the point of lower concentration. It is true that a potential measurement between those two points would show the one of lower concentration to be anodic, but that is merely because the measurement is between two oxygen half-cells of unequal force. The tendency for iron to corrode is the same at both points unless there is some difference in the surface coating or composition of the solution *apart from* concentration of dissolved oxygen.

A slight amount of corrosion will therefore occur on each surface. The greater concentration of oxygen at the outside will, however, result in more vigorous corrosion around the circumference, and in the rapid formation of a film of corrosion products, and a local alkaline condition. The protective effect thus exercised over the corroding metal will diminish its rate of solution, and cause the oxygen which is depositing there to search farther afield for a reactive anodic surface. This tendency is progressive because continued oxygen reaction, unaccompanied by an equivalent corrosion of metal over the same area, maintains an alkaline condition and a protective film. Conversely, the metal at the center of the drop has not had opportunity to build up its alkaline solution and protective film before all the corrosive action is localized upon it as the least protected surface available. Consequently the metal goes into solution without a corresponding formation of hydroxide in its immediate vicinity, the solution becomes acidic, no protective film can be built up, and all the corrosive action is localized towards the formation of a pit. Further aid to this tendency is furnished by a mantle of corrosion product built up where ferrous ions diffusing from the center meet hydroxide ions from the outside. This mantle shuts off oxygen which is diffusing in towards the center, but it is too far away from the metal to have any protective action.

Localized corrosion due indirectly to differences in oxygen concentration is of considerable practical importance. Familiar examples which are caused by this, at least in part, are the pitting of pipe threads and of steel covered with mill scale.

EFFECT OF VELOCITY

The experimental evidence on the effect of velocity in corrosion of steel by natural waters is contradictory. Heyn and Bauer[15] found that corrosion increased with velocity up to a certain critical point but that above this point there was a sharp decrease. Friend[16] obtained similar results in his experiments, although the critical velocity which he found was fifty times as great as that of Heyn and Bauer. Speller[17] on the other hand, finds a regular increase of corrosion with velocity, with no indication of a critical point of maximum activity over the ranges studied by Heyn and Bauer and by Friend.

It is difficult to explain these apparent contradictions. Unquestionably the difference in experimental methods is responsible for the difference in results. Heyn and Bauer and Friend used clean metal specimens, flowed the water past them, and determined corrosion rates from the losses in weight. Speller passed water through steel pipe, calculating his corrosion results from the amount of dissolved oxygen removed from the water by its passage through the pipe. Probably the most important difference is the complete absence of corrosion products at the start of the experiment in the first cases as compared to their presence in Speller's work.

Evans,[18] commenting on Friend's work, states: "It seems more likely that the falling off in the rate of corrosion at high water speeds is due to the fact that the more rapid stream insures uniform oxygen concentration over all parts of the surface." This implies the formation of a somewhat protective film of corrosion products over the whole surface—a film which reduces corrosion primarily because it does not break down locally to give strongly anodic spots of corroding metal. Evans' experiments to prove this theory are not conclusive and considerable experimental work is necessary to confirm the observations of a "critical" velocity

[15] Mitt. pgl. Materialprüfungsamt, **28**, 62 (1910).
[16] J. Chem. Soc., **119**, 932 (1921).
[17] J. I. E. C., **15**, 134, (1923).
[18] J. I. E. C., **17**, 363, (1925).

under a wide variety of conditions before any one explanation can be accepted.

Attempts to check Friend's results over the same velocity range have been made by rotating a vertical cylindrical test piece in distilled water.[19] The method of preparing the surface for testing was found to be a variable of greater importance than the speed of rotation. In a series of about six runs at varying velocities and with a uniform method of preparation by grinding with coarse emery, corrosion was found to increase with velocity with only one exception (which, incidentally, could not be duplicated in a later run). Speller's results definitely indicate that under practical conditions in the corrosion of pipe, corrosion increases continuously with velocity—a result which would be expected from the theory of oxygen diffusion if complications such as surface conditions and character of rust film are not superimposed and determinant.

In acid corrosion the effects of velocity are somewhat more definite. Friend's experiments in whirling a horizontal steel disc in sulfuric acid led him to conclude that the corrosion rate was directly proportional to the velocity and that different concentrations of acid give the same corrosion rates at the same velocity.

A more comprehensive study[20] of this problem has been made by rotating a vertical steel cylinder, thereby avoiding differences in velocities at different points on the surface. In general the corrosion rate at rest was higher than that at low velocity, but further increase in velocity raised the corrosion. Experiments with sulfuric acid varying from 0.004 to 5.0 normal showed that, while corrosion at rest varied nine-fold over this range of concentration, at high velocity the rate was practically the same for all strengths and therefore independent of concentration. Further experiments in which atmospheres of oxygen or of nitrogen were maintained over the acid showed that the corrosion at high velocity was due primarily to the action of oxygen dissolved in the acid, whereas the corrosion at rest was due chiefly to the action of the acid in liberating hydrogen gas. Increase in velocity reduced the amount

[19] Otto Rickers, M.S. Thesis M. I. T., 1922.
[20] Whitman, Russell, Welling, Cochrane, J. I. E. C., 15, 672 (1923).

of hydrogen gas evolved, possibly because the bubbles were smaller in size and therefore required more work for their formation. Conversely, increase in velocity allowed faster oxygen reaction by speeding up diffusion processes.

The effect of velocity on protective films is unquestionably an important factor in certain cases. It is now generally admitted that many examples of so-called "erosion" are really corrosion phenomena in which the protective film of corrosion products is removed by the high velocity. Whitney,[21] in studying the corrosion on steam turbine buckets by testing samples in a water-splashing device, found that the substitution of hydrogen for air in the system eliminated all traces of the corrosive or "erosive" action. He states, "Between the extreme case of eroded propellers" (which Whitney admits is mechanical action) "and simple chemical corrosion there is a large field of destruction of metals in which the action commonly spoken of as mechanical erosion is more probably chemical corrosion, with subsequent removal of the new compound by erosion."

A striking example of this effect is shown in the corrosion of steel by concentrated sulfuric acid.[22] At rest, the steel samples were practically unattacked by 100 per cent acid, but when they were rotated at a velocity of 60 cm. per second the corrosion was severe, particularly where the sample rubbed against its glass supporting rod. At such points the penetration was as great as 0.3 cm. in 72 hours. Samples which had been previously treated by quiet immersion in the same acid (thereby building up a protective film) showing an initial resistance to attack at high velocity and corroded only half as much as did the untreated samples. The authors conclude that: "This phenomenon further confirms the concept that the low corrosion at rest is due to film protection and that the acceleration with velocity is largely the result of removing the film. The presence of solid corrosion products suspended in the acid probably has a further effect of the same general nature."

[21] J. I. E. C., **17**, 385 (1925).
[22] Whitman and Russell, J. I. E. C., **17, 348** (1925).

EFFECT OF DISSOLVED SALTS

Friend [23] has reported an extensive series of beaker tests on iron in neutral salt solutions, using the results to support his theory of catalytic acceleration of corrosion by the colloidal corrosion products. In these tests, however, other factors besides the specific action of the salt on corrosion are involved. Thus Friend himself points out in a later paper that the presence of the salt not only changes the solubility of oxygen in the solution, but that it also changes the specific rate of oxygen absorption. For authority on this latter point he refers to the excellent work of Adeney and Becker on the rate of solution of atmospheric gases by water.

The results of beaker tests are therefore inconclusive since the changes in gas absorption and solubility may have a much greater influence on the result than the specific effect of the salt itself.

Evans attempts to avoid the complications of variable rate of gas absorption in a beaker test by studying the action of drops of salt solution placed on a clean metal surface. It would seem, however, that the results of such tests would also be of limited applicability, since the degree of convection within the drop would certainly vary with the nature and concentration of the salt.

A few tests[24] on the corrosiveness of salt solutions flowing through steel pipe have been made by the oxygen drop method. In these tests the effects of rate of oxygen solution and of variable convection velocities as a function of the solution are presumably eliminated. While the conditions do not parallel those existing during water-line or spray corrosion they represent the many cases where metal is completely submerged in salt solution.

In this same work the solubility of ferrous hydroxide in distilled water and in the various salt solution was determined. The authors emphasize the parallel effect of the salt in reducing corrosion and in reducing the solubility of ferrous hydroxide, ad-

[23] Carnegie Scholarship Mem., 11, (1922).
[24] Whitman, Russell and Davis, J. A. C. S., 47, 70 (1925).

vancing the theory that the specific effect of the salt on corrosion is to change the solubility of the initial product of corrosion. If this is rendered less soluble it precipitates closer to the metal surface and forms a more adherent and protective film. Conversely, a salt which increases the solubility makes the film less protective and increases the rate of corrosion.

The effect of salts in localizing corrosion may be evidenced in two directions. In the first place, by greatly increasing the conductivity of the solution, they lengthen the distance over which an electrochemical cell can operate. This makes it possible for a large cathode area to concentrate its corrosive activity upon a small unprotected anode area and cause rapid pitting.

In the second place those salts which cause the formation of protective films may accentuate pitting to a marked degree under certain circumstances. It seems to be generally true that a tendency towards greater film protection increases the tendency toward localization of corrosion. Thus the pitting of iron in dilute solutions of sodium carbonate has been noted by Lyon[25] and others. The addition of excess lime to calcium brines and of cautic soda to sodium brines, while it reduces corrosion, actually increases pitting to a marked degree.[26] Evidently the major part of the surface is protected but certain localized spots are left exposed to concentrated attack, just as the iron exposed by a pinholen in tin plate suffers rapid corrosion because of the large active area of cathodic tin surrounding it.

The close relationship between passivity and the formation of protective films is becoming more evident as the result of these studies. The action of alkalies on iron has been termed "passivifying"—it is now known to be the result of protective film formation due to decreased solubility of the corrosion product.[27] Chromates have been shown to render iron hydroxides practically insoluble in water. Steel in concentrated sulfuric acid is still another instance of passivity where the evidence for the action of

[25] Lyon, J. Am. Soc. Nav. Eng., **24**, 845 (1912).

[26] Whitman, Chappell and Roberts, Refrig. Eng., **12**, 158 (1925).

[27] Speller and Texter, loc. cit.

  Whitman, Russell and Altieri, loc. cit.

protective film is reasonably convincing. While there are still many cases which have not been subjected to critical examination in the light of the film theory, the concept may be accepted as a practical working basis for further investigation of such problems. In particular, its application to the development of alloys resistant to strongly oxidizing conditions may indicate the answer to many problems which are as yet unsolved.

SUMMARY

The electrochemical theory is now generally accepted as most adequately explaining corrosion phenomena at ordinary temperatures.

The presence of dissolved oxygen is necessary for appreciable corrosion in so many cases that the nature and character of its reaction are matters of primary importance. The rate of diffusion of oxygen to an effective cathode surface frequently determines the rate of corrosion. Variations in oxygen concentration between different points on the surface, if maintained for a considerable time, lead to effects which result in localized corrosion and pitting.

The usual effect of velocity is to increase corrosion due to dissolved oxygen, both by increasing diffusion and by breaking down protective films. Certain results which indicate a maximum in the plot of corrosion against velocity in natural waters have not been satisfactorily explained.

The effect of dissolved salts on the rate of corrosion may be intimately related to the manner in which they affect the solubility of the corrosion product. The presence of dissolved salts often increases the pitting tendency. This is due both to the increased conductivity of the solution, and, in the case of salts which reduce corrosion, to the tendency for large portions of the surface to become protected themselves and to concentrate their activity upon small unprotected anodic areas. Certain "passivity" phenomena are evidently due to protective film formation and it seems possible that the concept of protective films may be adapted to all cases of passivity.